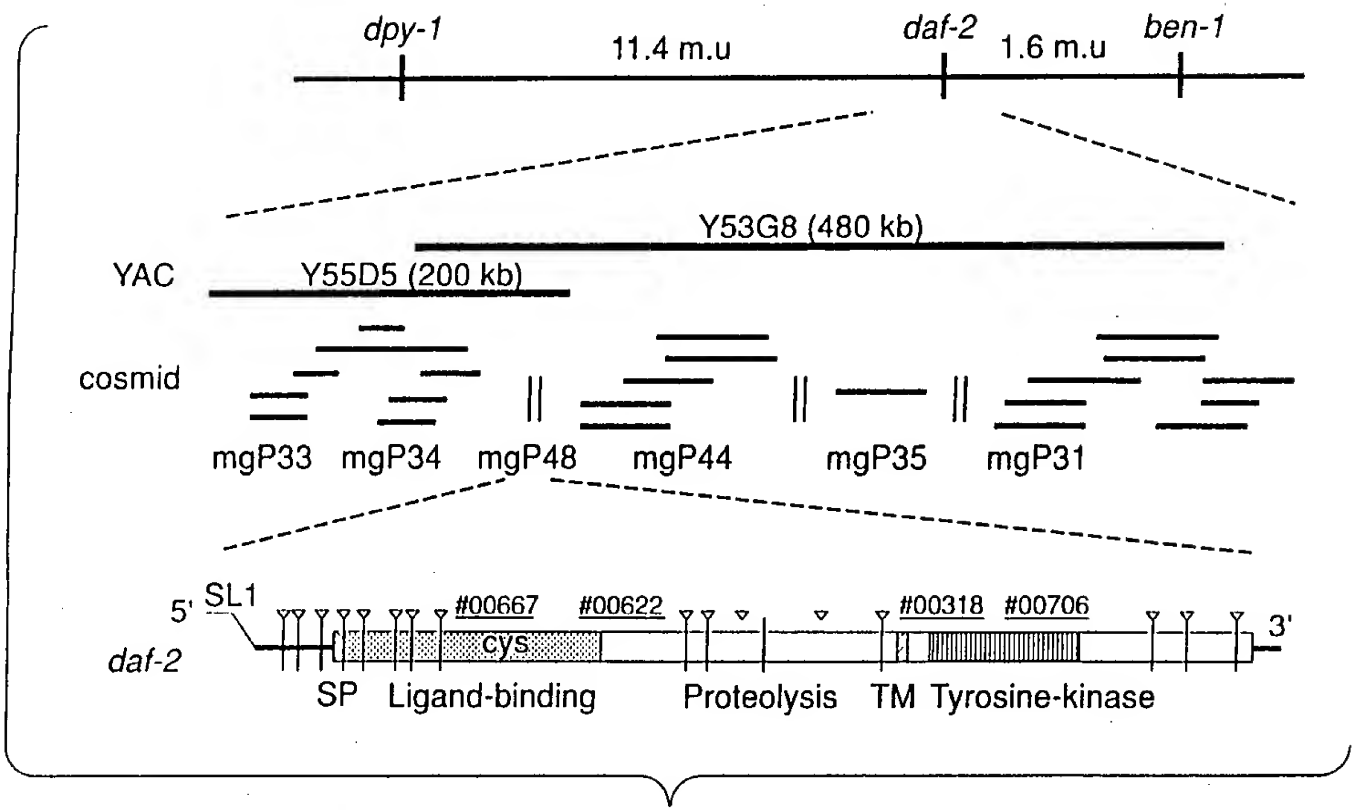
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cys
SP
Ligand-binding
Proteolysis
TM
Tyrosine-kinase

Fig. 1

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Fig. 2A

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Fig. 2B (sheet 1 of 3)

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Fig. 2B (sheet 2 of 3)

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Fig. 2B (sheet 3 of 3)

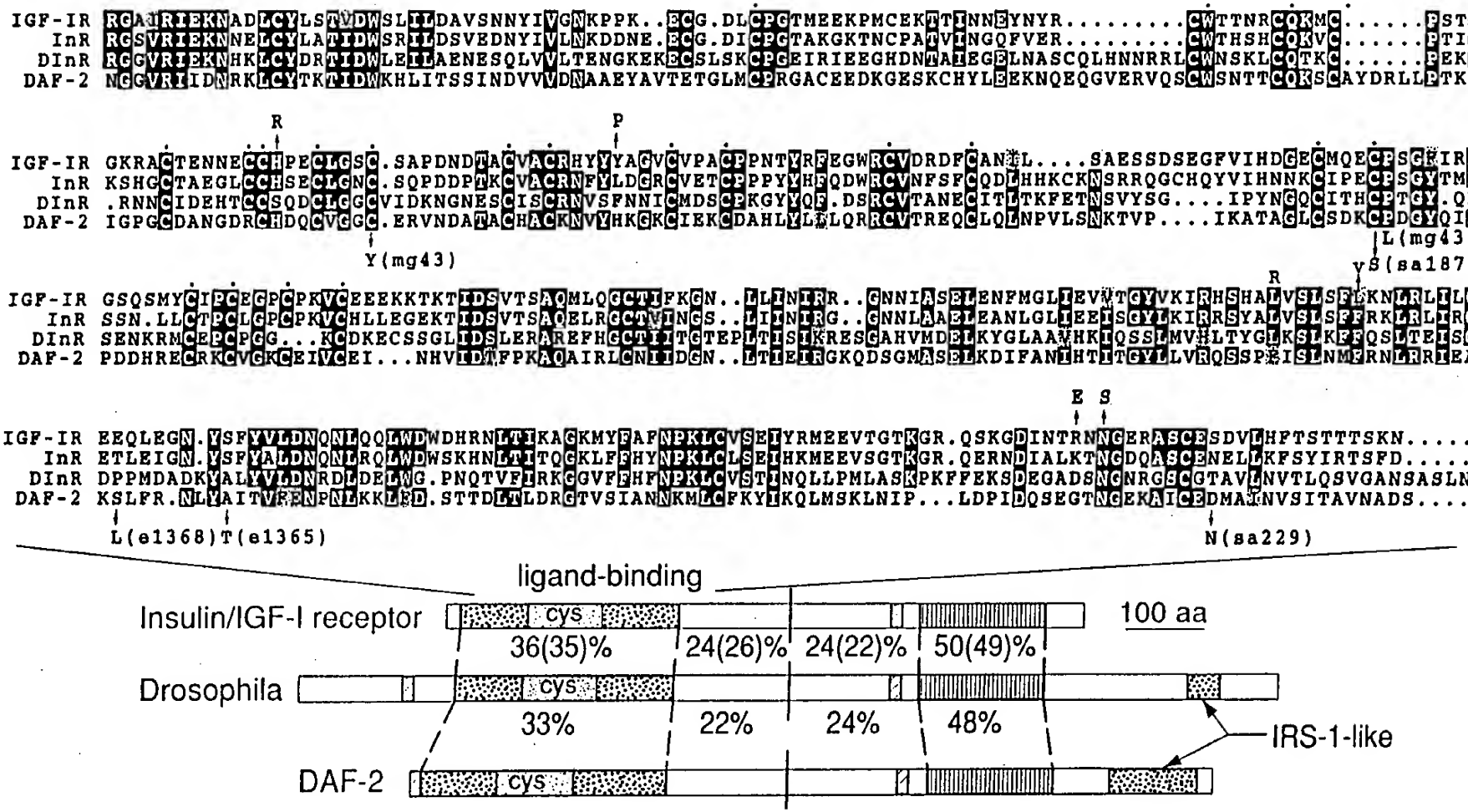


Fig. 2C (sheet 1 of 2)

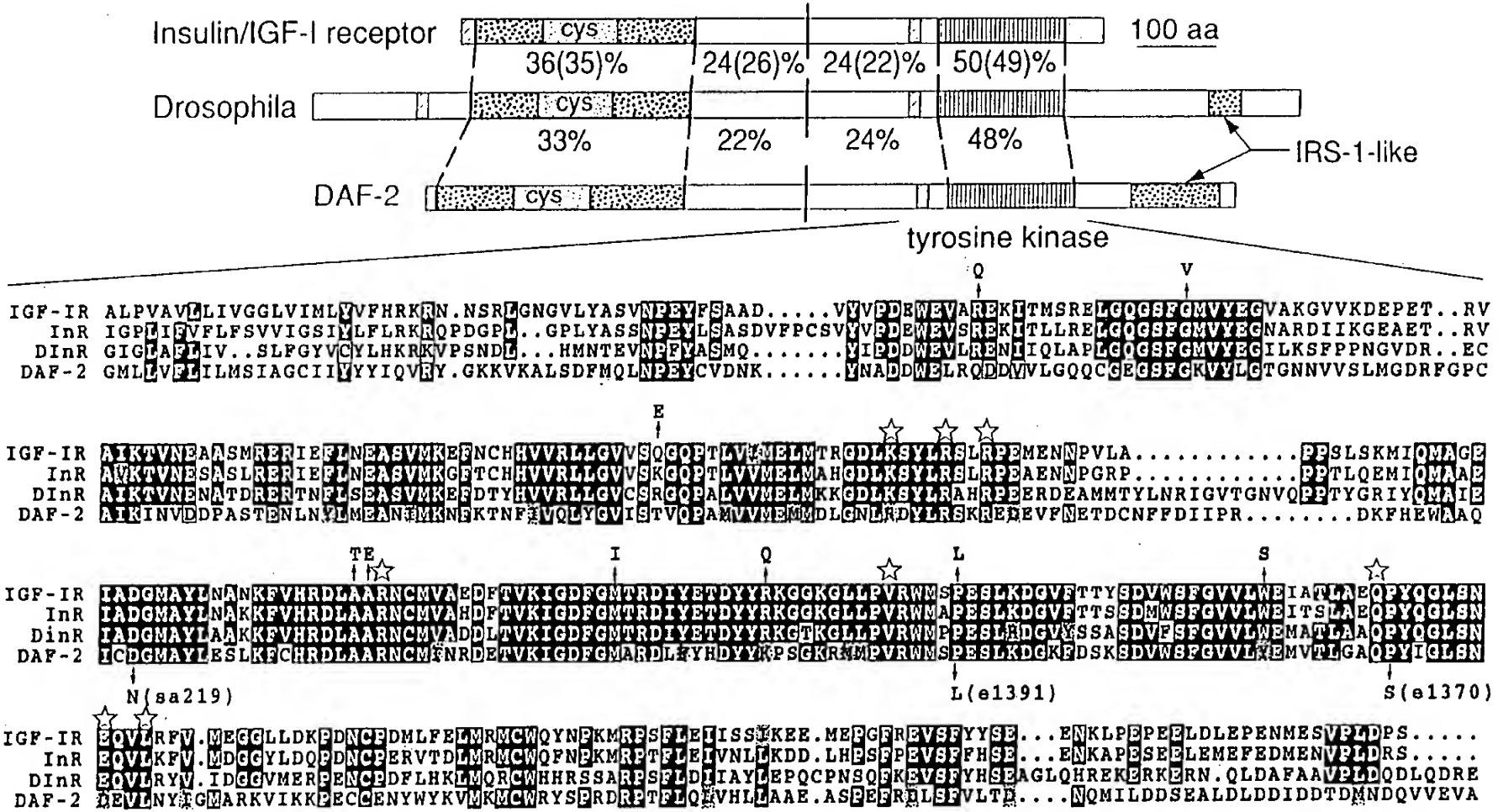
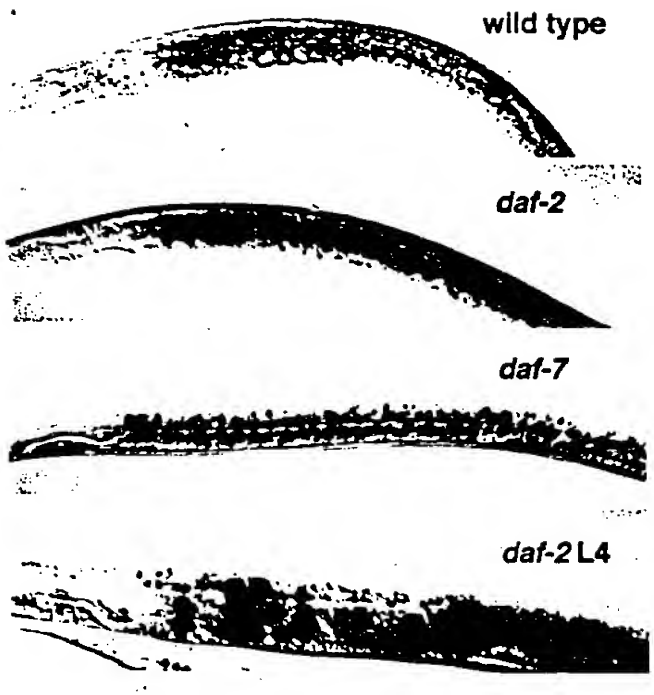


Fig. 2C (sheet 2 of 2)



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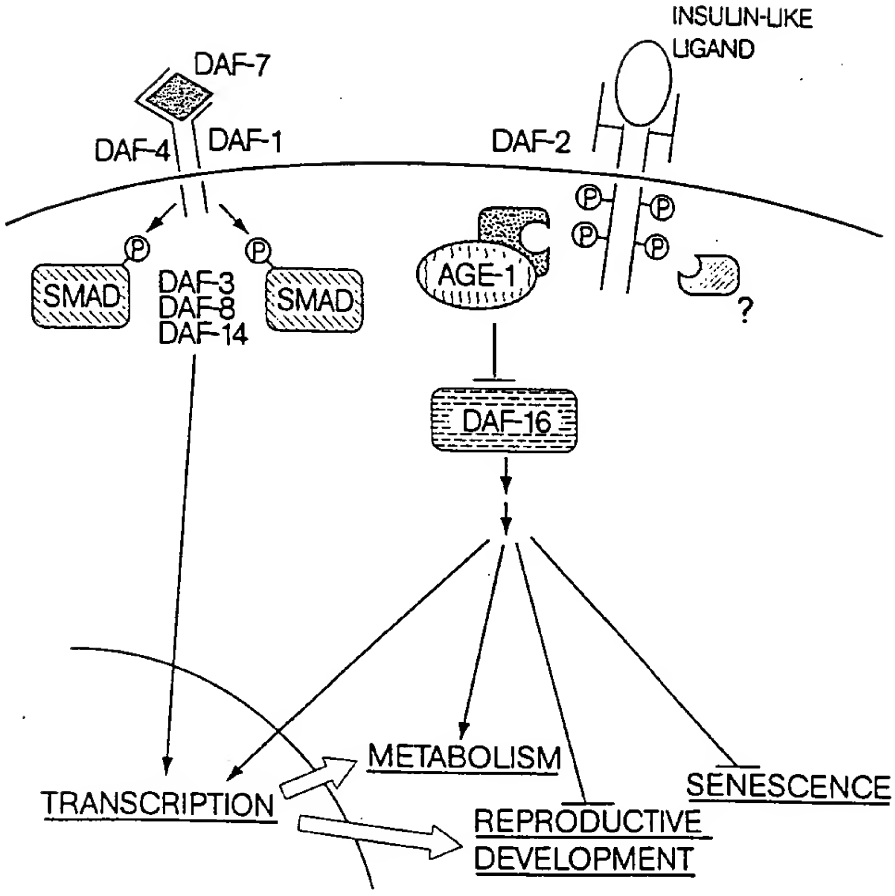
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DAF-4
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DAF-2
P
SMAD
DAF-3
DAF-8
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SMAD
AGE-1
?
DAF-16
TRANSCRIPTION
METABOLISM
SENESCENCE
REPRODUCTIVE
DEVELOPMENT

Fig. 4

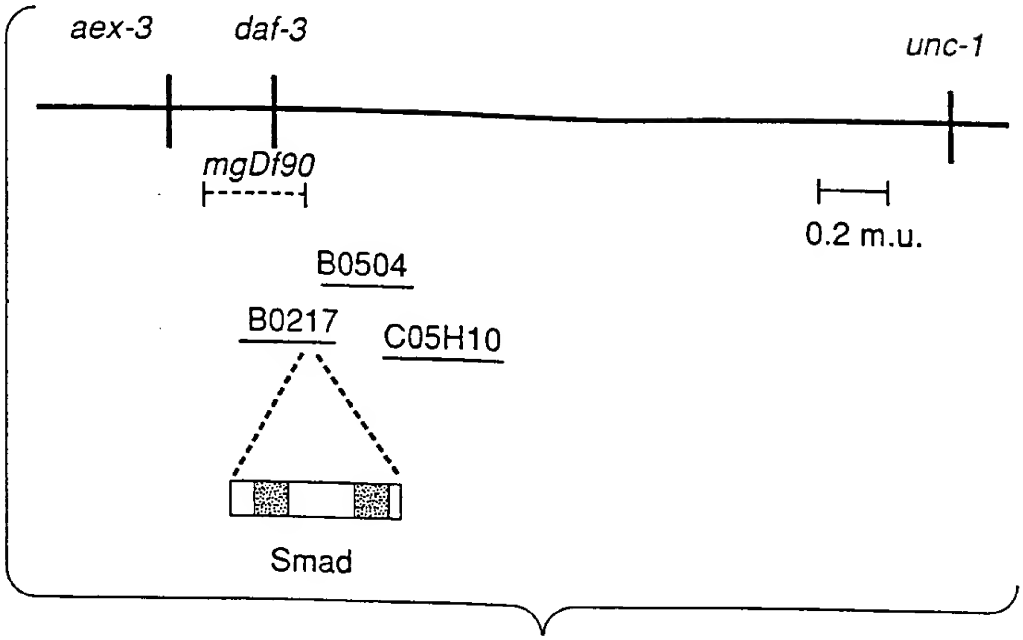
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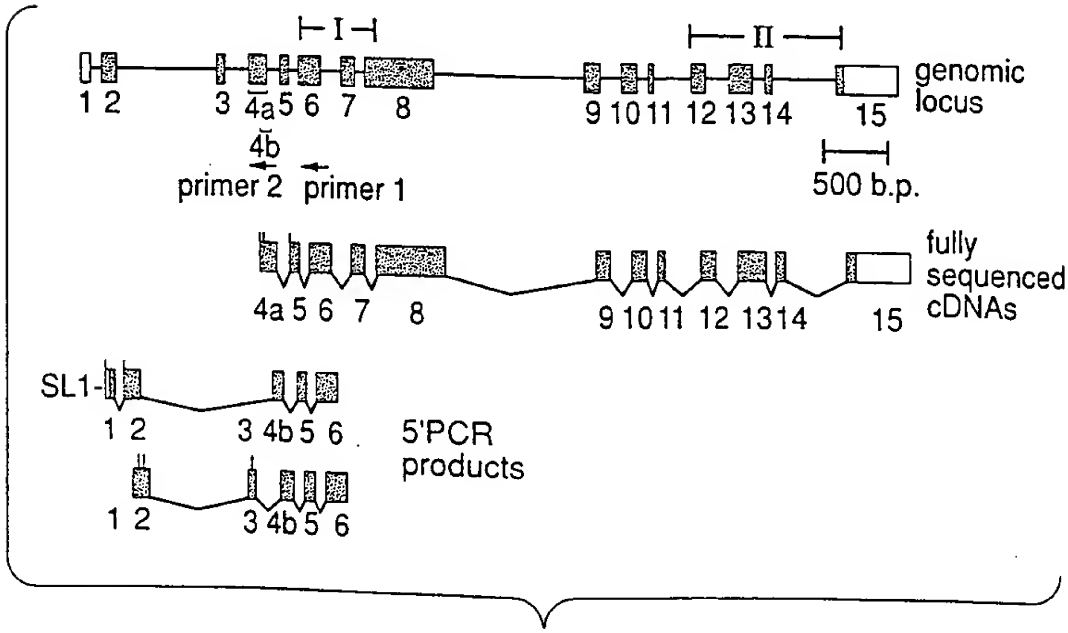
Fig. 5A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II
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primer 2
primer 1
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fully sequenced cDNAs
SL1-
1 2 3 4b 5 6
5'PCR products
1 2 3 4b 5 6

Fig. 5B

Domain I

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DPC4    GGESETFAKRAIESLVKKLKEKKDELDSLITAITTNGAHPSKCVTIQRTLDG
             mg125 P->L
        RLQVHGRKGFPHVVYGKLWRFNEMTKNETRHVDHCKHAFEMKSDMVCVNPYH
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Domain II

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      mg132  G->E
        RKAIVDGIRFSYKKDGSVWLQNRMKYPVFVTSGYLDEQSGGLKKDKVHKVYGCA
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Fig. 5C

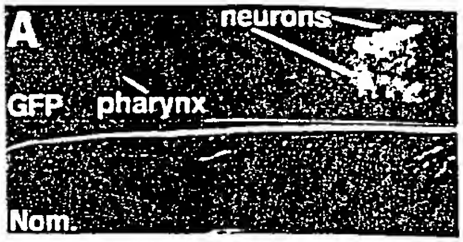


Fig. 6A

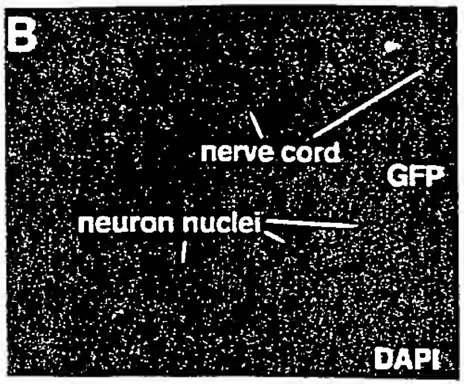


Fig. 6B

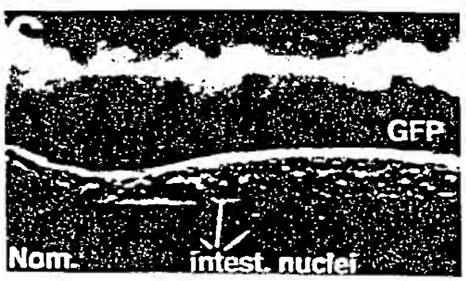


Fig. 6C

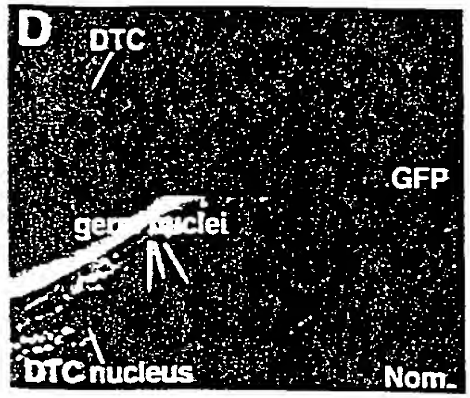


Fig. 6D

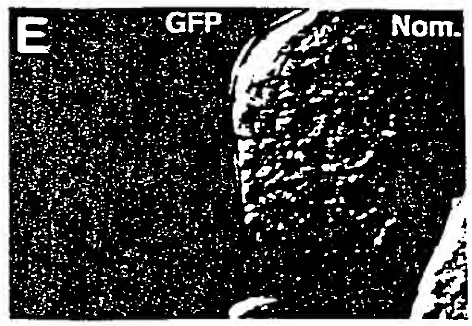


Fig. 6E

Fig. 6F

Fig. 6G

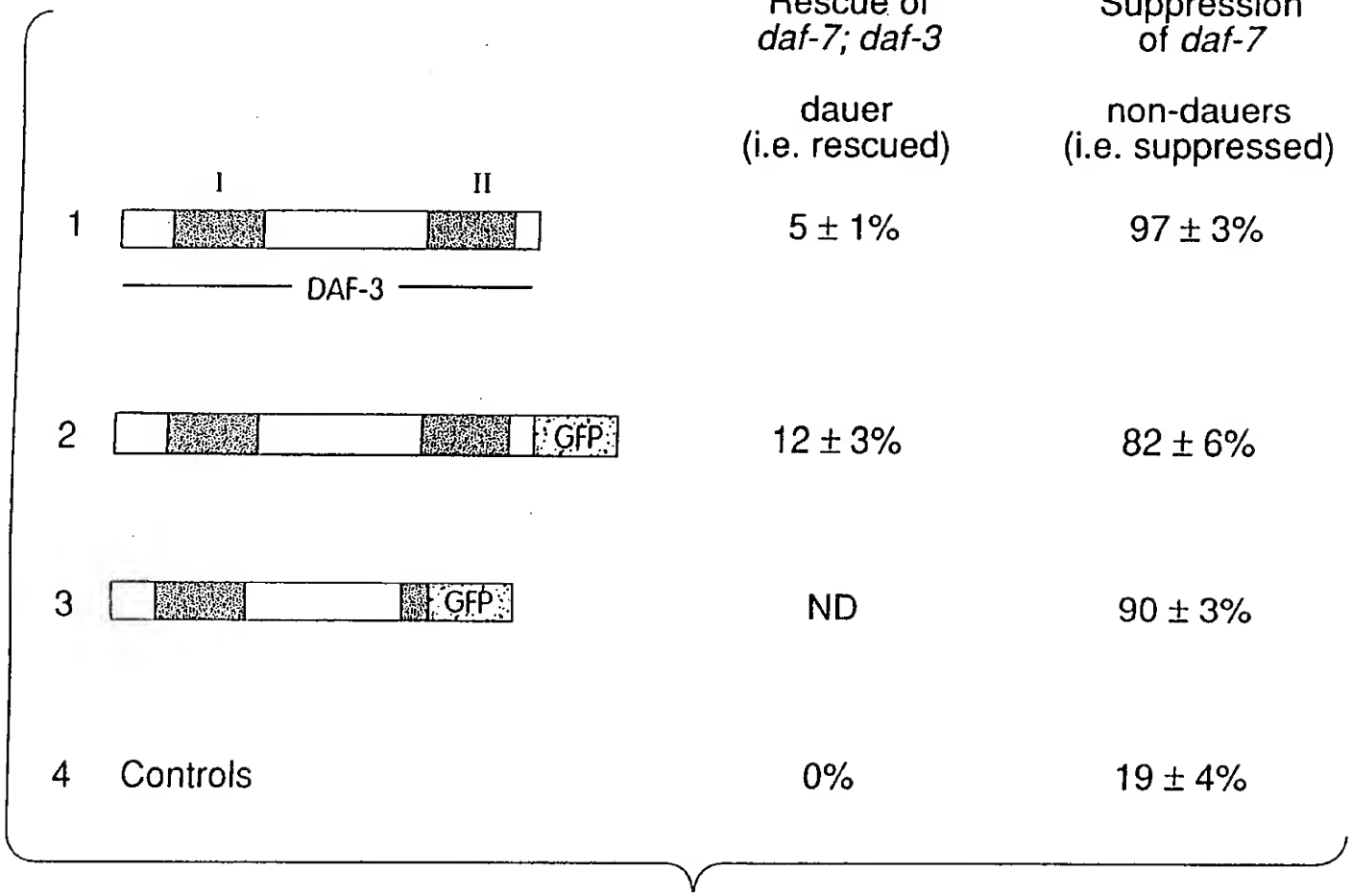

Rescue of
daf-7; daf-3
dauer
(i.e. rescued)
Suppression
of daf-7
non-dauers
(i.e. suppressed)
I
II
1
DAF-3
5 ± 1%
97 ± 3%
2
GFP
12 ± 3%
82 ± 6%
3
GFP
ND
90 ± 3%
4
Controls
0%
19 ± 4%

Fig. 7

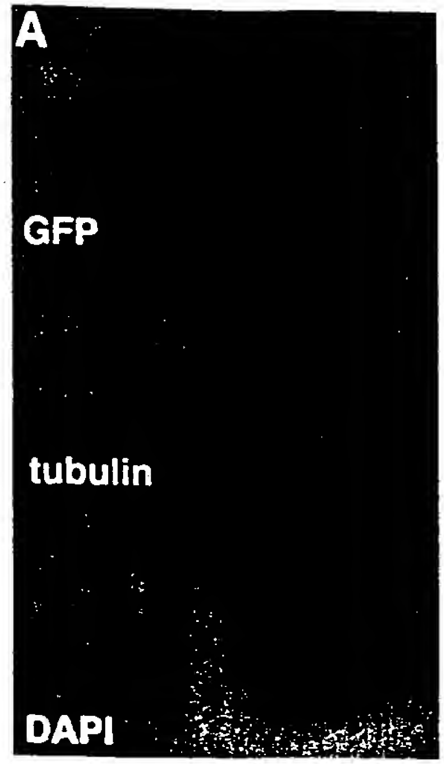


Fig. 8A

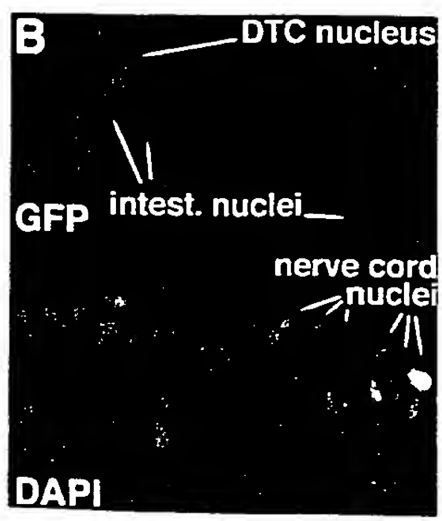
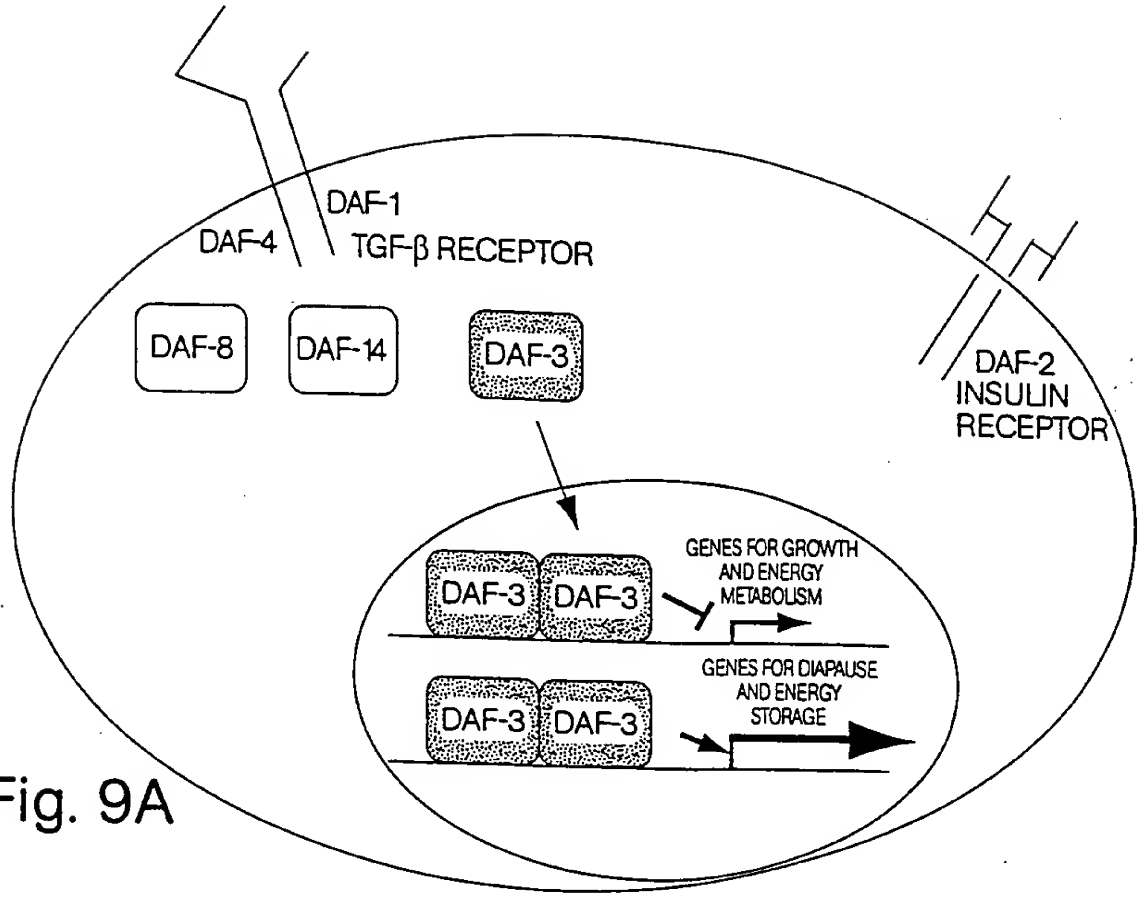


Fig. 8B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TGF-β RECEPTOR
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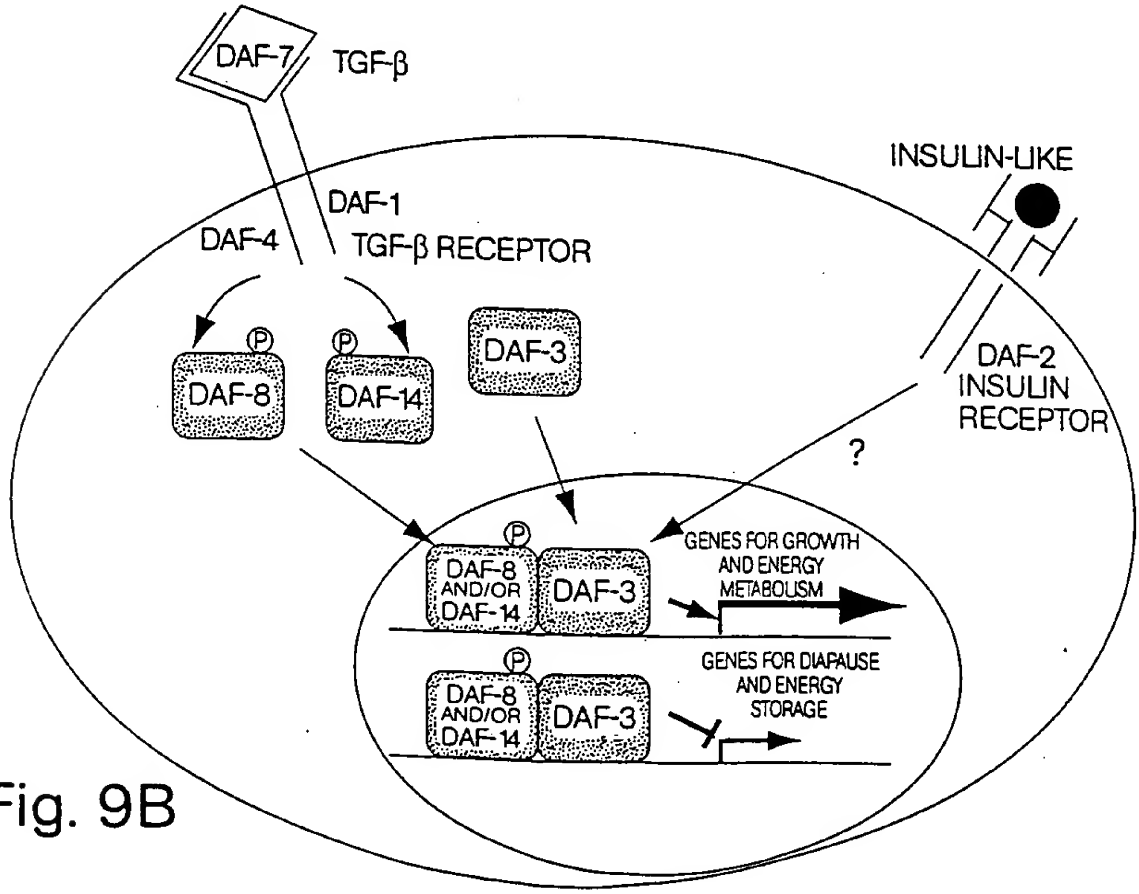
RECEPTOR
DAF-3
DAF-3
GENES FOR GROWTH
AND ENERGY
METABOLISM
DAF-3
DAF-3
GENES FOR DIAPAUSE
AND ENERGY
STORAGE

Fig. 9A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DAF-8
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DAF-3
DAF-2
INSULIN
RECEPTOR
?
P
DAF-8
AND/OR
DAF-14
DAF-3
GENES FOR GROWTH
AND ENERGY
METABOLISM
P
DAF-8
AND/OR
DAF-14
DAF-3
GENES FOR DIAPAUSE
AND ENERGY
STORAGE

Fig. 9B

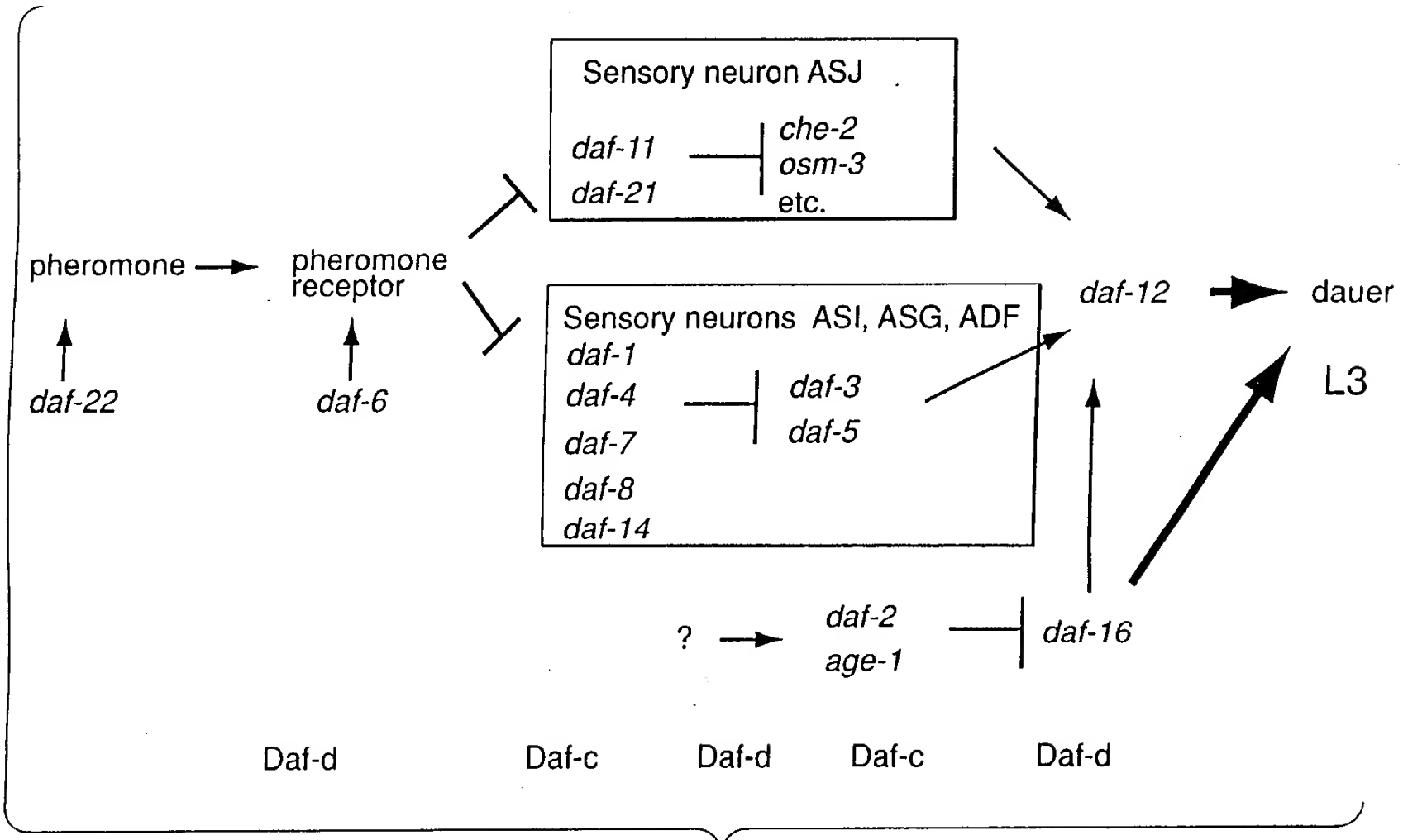
Sensory neuron ASJ
daf-11
daf-21
che-2
osm-3
etc.
pheromone
pheromone receptor
daf-22
daf-6
Sensory neurons ASI, ASG, ADF
daf-1
daf-4
daf-7
daf-8
daf-14
daf-3
daf-5
daf-12
dauer
L3
?
daf-2
age-1
daf-16
Daf-d
Daf-c
Daf-d
Daf-c
Daf-d

Fig. 10

```
1    atgaagctaa tagcaacttc tcttctagtt cccgacgagc acacaccgat
51   gatgtcacca gtgaatacaa ctacaaagat tctacaacgg agtggtatta
101  aaatggaaat cccgccatat ttggatccag acagtcagga tgatgacccg
151  gaagatggtg tcaactaccc ggatccagat ttatttgaca caaaaaacac
201  aaatatgacc gagtacgatt tggatgtgtt gaagcttgga aaaccagcag
251  tagatgaagc acggaaaaag atcgaagttc ccgacgctag tgcgccgcca
301  aacaaaattg tagaatattt gatgtattat agaacgttaa aagaaagtga
351  actcatacaa ctgaatgcgt atcggacaaa acgaaatcga ttatcgttga
401  acttggtcaa aaacaatatt gatcgagagt tcgaccaaaa agcttgcgag
451  tccctggtga aaaaattgaa ggataagaag aatgatctcc agaacctgat
501  tgatgtggtt ctttcaaaag gtacaaaata taccggttgc attacaattc
551  caaggacact tgatggccgg ttacaggtcc acggaagaaa aggtttccct
601  cacgtagtct atggcaaact gtggaggttt aatgaaatga caaaaaacga
651  aacgcgtcat gtggaccact gcaagcacgc atttgaaatg aaaagtgaca
701  tggtatgcgt gaatccctat cactacgaaa ttgtcattgg aactatgatt
751  gttgggcaga gggatcatga caatcgagat atgccgccgc cacatcaacg
801  ctaccacact ccaggtcggc aggatccagt tgacgatatg agtagattta
851  taccaccagc ttccattcgt ccgcctccga tgaacatgca cacaaggcct
901  cagcctatgc ctcaacaatt gccttcagtt ggcgcaacgt ttgcccatcc
951  tctcccacat caggcgccac ataacccagg ggtttcacat ccgtactcca
1001 ttgctccaca gacccattac ccgttgaaca tgaacccaat tccgcaaatg
1051 ccgcaaatgc cacaaatgcc accacctctc catcagggat atggaatgaa
1101 tgggccgagt tgctcttcag aaaacaacaa tccattccac caaaatcacc
1151 attataatga tattagccat ccaaatcact attcctacga ctgtggtccg
1201 aacttgtacg ggtttccaac tccttatccg gattttcacc atcctttcaa
1251 tcagcaacca caccagccgc cacaactatc acaaaaccat acgtcccaac
1301 aaggcagtca tcaaccaggg caccaaggtc aggtaccgaa tgatccacca
1351 atttcaagac cagtgttaca accatcaaca gtcaccttgg acgtgttccg
1401 tcggtactgt agacagacat ttggaaatcg attttttgaa ggagaaagtg
1451 aacaatccgg cgcaataatt cggtctagta acaaattcat tgaagaattt
1501 gattcgccga tttgtggtgt gacagttgtt cgaccgcgga tgacagacgg
1551 tgaggttttg gagaacatca tgccggaaga tgcaccatat catgacattt
1601 gcaagttcat tttgaggctc acatcagaaa gtgtaacttt ctcaggagag
1651 gggccagaag ttagtgattt gaacgaaaaa tggggaacaa ttgtgtacta
1701 tgagaaaaat ttgcaaattg gcgagaaaaa atgttcgaga ggaaatttcc
1751 acgtggatgg cggattcatt tgctctgaga atcgttacag tctcggactt
1801 gagccaaatc caattagaga accagtggcg tttaaagttc gtaaagcaat
1851 agtggatgga attcgctttt cctacaaaaa agacgggagt gtttggcttc
1901 aaaaccgcat gaagtacccg gtatttgtca cttctgggta tctcgacgag
1951 caatcaggag gcctaaagaa ggataaagtg cacaaagttt acggatgtgc
2001 gtctatcaaa acgtttggct tcaacgtttc caaacaaatc atcagagacg
2051 cgcttctttc caagcaaatg gcaacaatgt acttgcaagg aaaattgact
```

Fig. 11A (sheet 1 of 2)

```
2101  ccgatgaatt atatctacga gaagaagact caggaagagc tgcgaaggga
2151  agcaacacgc accactgatt cattggccaa gtactgttgt gtccgtgtct
2201  cgttctgcaa aggatttgga gaagcatacc cagaacgccc gtcaattcat
2251  gattgtccag tttggattga gttgaaaatc aacattgcct acgatttcat
2301  ggattcaatc tgccagtaca taaccaactg cttcgagccg ctaggaatgg
2351  aagattttgc aaaattggga atcaacgtca gtgatgacta aatgataact
2401  tttttcactc accctactag atactgattt agtcttattc caaatcatcc
2451  aacgatatca aacttttcc tttgaacttt gcatactatg ttatcacaag
2501  ttccaagcag tttcaataca aacataggat atgttaacaa cttttgataa
2551  gaatcaagtt accaactgtt cattgtgagc tttgagctgt atagaaggac
2601  aatgtatccc atacctcaat ctttaatagt catcagtcac tggtcccgca
2651  ccaatttttt cgattcgcat atgtcatata ttgcaccgtg gccctttta
2701  ttgtaacttt taatatattt tcttcccaac ttgtgaatat gattgatgaa
2751  ccaccatttt gagtaataaa tgtatttttt gtgg
```

Fig. 11A (sheet 2 of 2)

```
   1 gtaatcaaat tgtaaaggaa aaatattaat agtcagagta cacataaatg
  51 ggtgatcatc ataatttaac gggccttccc ggtacctcca tcccgccaca
 101 gttcaactat tctcagcccg gtaccagcac cggaggcccg ctttatggtg
 151 gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag
 201 aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa
 251 tatggctaat gttcccgacg agcacacacc gatgatgtca ccagtgaata
 301 caactacaaa gattctacaa cggagtggta ttaaaatgga aatcccgcca
 351 tatttggatc cagacagtca ggatgatgac ccggaagatg gtgtcaacta
 401 cccggatcca gatttatttg acacaaaaaa cacaaatatg accgagtacg
 451 atttggatgt gttgaagctt ggaaaaccag cagtagatga agcacggaaa
 501 aagatcgaag ttccccgacgc tagtgcgccg ccaaacaaaa ttgtagaata
 551 tttgatgtat tatagaacgt taaaagaaag tgaactcata caactgaatg
 601 cgtatcggac aaaacgaaat cgattatcgt tgaacttggt caaaaacaat
 651 attgatcgag agttcgacca aaaagcttgc gagtccctgg tgaaaaaatt
 701 gaaggataag aagaatgatc tccagaacct gattgatgtg gttctttcaa
 751 aaggtacaaa atataccggt tgcattacaa ttccaaggac acttgatggc
 801 cggttacagg tccacggaag aaaaggtttc cctcacgtag tctatggcaa
 851 actgtggagg tttaatgaaa tgacaaaaaa cgaaacgcgt catgtggacc
 901 actgcaagca cgcatttgaa atgaaaagtg acatggtatg cgtgaatccc
 951 tatcactacg aaattgtcat tggaactatg attgttgggc agaggatca
1001 tgacaatcga gatatgccgc cgccacatca acgctaccac actccaggtc
1051 ggcaggatcc agttgacgat atgagtagat ttataccacc agcttccatt
1101 cgtccgcctc cgatgaacat gcacacaagg cctcagccta tgcctcaaca
1151 attgccttca gttggcgcaa cgtttgccca tcctctccca catcaggcgc
1201 cacataaccc aggggtttca catccgtact ccattgctcc acagacccat
1251 tacccgttga acatgaaccc aattccgcaa atgccgcaaa tgccacaaat
1301 gccaccacct ctccatcagg gatatggaat gaatgggccg agttgctctt
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1401 catccaaatc actattccta cgactgtggt ccgaacttgt acgggtttcc
1451 aactccttat ccggattttc accatccttt caatcagcaa ccacaccagc
1501 cgccacaact atcacaaaac catacgtccc aacaaggcag tcatcaacca
1551 gggcaccaag gtcaggtacc gaatgatcca ccaatttcaa gaccagtgtt
1601 acaaccatca acagtcacct tggacgtgtt ccgtcggtac tgtagacaga
1651 catttggaaa tcgatttttt gaaggagaaa gtgaacaatc cggcgcaata
1701 attcggtcta gtaacaaatt cattgaagaa tttgattcgc cgatttgtgg
1751 tgtgacagtt gttcgaccgc ggatgacaga cggtgaggtt ttggagaaca
1801 tcatgccgga agatgcacca tatcatgaca tttgcaagtt cattttgagg
1851 ctcacatcag aaagtgtaac tttctcagga gaggggccag aagttagtga
1901 tttgaacgaa aaatggggaa caattgtgta ctatgagaaa aatttgcaaa
1951 ttggcgagaa aaaatgttcg agaggaaatt tccacgtgga tggcggattc
2001 atttgctctg agaatcgtta cagtctcgga cttgagccaa atccaattag
2051 agaaccagtg gcgtttaaag ttcgtaaagc aatagtggat ggaattcgct
```

Fig. 11B (sheet 1 of 2)

```
2101  tttcctacaa aaaagacggg agtgtttggc ttcaaaaccg catgaagtac
2151  ccggtatttg tcacttctgg gtatctcgac gagcaatcag gaggcctaaa
2201  gaaggataaa gtgcacaaag tttacggatg tgcgtctatc aaaacgtttg
2251  gcttcaacgt ttccaaacaa atcatcagag acgcgcttct ttccaagcaa
2301  atggcaacaa tgtacttgca aggaaaattg actccgatga attatatcta
2351  cgagaagaag actcaggaag agctgcgaag ggaagcaaca cgcaccactg
2401  attcattggc caagtactgt tgtgtccgtg tctcgttctg caaaggattt
2451  ggagaagcat acccagaacg cccgtcaatt catgattgtc cagtttggat
2501  tgagttgaaa atcaacattg cctacgattt catggattca atctgccagt
2551  acataaccaa ctgcttcgag ccgctaggaa tggaagattt tgcaaaattg
2601  ggaatcaacg tcagtgatga ctaaatgata actttttca ctcaccctac
2651  tagatactga tttagtctta ttccaaatca tccaacgata tcaaactttt
2701  tcctttgaac tttgcatact atgttatcac aagttccaag cagtttcaat
2751  acaaacatag gatatgttaa caacttttga taagaatcaa gttaccaact
2801  gttcattgtg agctttgagc tgtatagaag gacaatgtat cccatacctc
2851  aatctttaat agtcatcagt cactggtccc gcaccaattt tttcgattcg
2901  catatgtcat atattgcacc gtggcccttt ttattgtaac ttttaatata
2951  ttttcttccc aacttgtgaa tatgattgat gaaccaccat tttgagtaat
3001  aaatgtattt tttgtgg
```

Fig. 11B (sheet 2 of 2)

1 gtaatcaaat tgtaaaggaa aaatattaat agtcagagta cacataaatg
51 ggtgatcatc ataatttaac gggccttccc ggtacctcca tcccgccaca
101 gttcaactat tctcagcccg gtaccagcac cggaggcccg ctttatggtg
151 gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag
201 aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa
251 tatggctaat gaatttaaac caataatcac attggacacg aaaccacctc
301 gtgatgccaa caagtcattg gcattcaatg gcgggttgaa gctaatcact
351 ccgaaaactg aagttcccga cgagcacaca ccgatgatgt caccagtgaa
401 tacaactaca aagattctac aacggagtgg tattaaaatg gaaatcccgc
451 catatttgga tccagacagt caggatgatg acccggaaga tggtgtcaac
501 tacccggatc cagatttatt tgacacaaaa aacacaaata tgaccgagta
551 cgatttggat gtgttgaagc ttggaaaacc agcagtagat gaagcacgga
601 aaaagatcga agttcccgac gctagtgcgc cgccaaacaa aattgtagaa
651 tatttgatgt attatagaac gttaaaagaa agtgaactca tacaactgaa
701 tgcgtatcgg acaaaacgaa atcgattatc gttgaacttg gtcaaaaaca
751 atattgatcg agagttcgac caaaaagctt gcgagtccct ggtgaaaaaa
801 ttgaaggata agaagaatga tctccagaac ctgattgatg tggttctttc
851 aaaaggtaca aaatataccg gttgcattac aattccaagg acacttgatg
901 gccggttaca ggtccacgga agaaaaggtt tccctcacgt agtctatggc
951 aaactgtgga ggtttaatga aatgacaaaa aacgaaacgc gtcatgtgga
1001 ccactgcaag cacgcatttg aaatgaaaag tgacatggta tgcgtgaatc
1051 cctatcacta cgaaattgtc attggaacta tgattgttgg gcagagggat
1101 catgacaatc gagatatgcc gccgccacat caacgctacc acactccagg
1151 tcggcaggat ccagttgacg atatgagtag atttatacca ccagcttcca
1201 ttcgtccgcc tccgatgaac atgcacacaa ggcctcagcc tatgcctcaa
1251 caattgcctt cagttggcgc aacgtttgcc catcctctcc cacatcaggc
1301 gccacataac ccaggggttt cacatccgta ctccattgct ccacagaccc
1351 attacccgtt gaacatgaac ccaattccgc aaatgccgca aatgccacaa
1401 atgccaccac ctctccatca gggatatgga atgaatgggc cgagttgctc
1451 ttcagaaaac aacaatccat tccaccaaaa tcaccattat aatgatatta
1501 gccatccaaa tcactattcc tacgactgtg gtccgaactt gtacgggttt
1551 ccaactcctt atccggattt tcaccatcct ttcaatcagc aaccacacca
1601 gccgccacaa ctatcacaaa accatacgtc ccaacaaggc agtcatcaac
1651 cagggcacca aggtcaggta ccgaatgatc caccaatttc aagaccagtg
1701 ttacaaccat caacagtcac cttggacgtg ttccgtcggt actgtagaca
1751 gacatttgga aatcgatttt ttgaaggaga aagtgaacaa tccggcgcaa
1801 taattcggtc tagtaacaaa ttcattgaag aatttgattc gccgatttgt
1851 ggtgtgacag ttgttcgacc gcggatgaca gacggtgagg ttttggagaa
1901 catcatgccg gaagatgcac catatcatga catttgcaag ttcattttga
1951 ggctcacatc agaaagtgta actttctcag gagaggggcc agaagttagt
2001 gatttgaacg aaaaatgggg aacaattgtg tactatgaga aaaatttgca
2051 aattggcgag aaaaaatgtt cgagaggaaa tttccacgtg gatggcggat

Fig. 11C (sheet 1 of 2)

2101 tcatttgctc tgagaatcgt tacagtctcg gacttgagcc aaatccaatt
2151 agagaaccag tggcgtttaa agttcgtaaa gcaatagtgg atggaattcg
2201 cttttcctac aaaaaagacg ggagtgtttg gcttcaaaac cgcatgaagt
2251 acccggtatt tgtcacttct gggtatctcg acgagcaatc aggaggccta
2301 aagaaggata aagtgcacaa agtttacgga tgtgcgtcta tcaaaacgtt
2351 tggcttcaac gtttccaaac aaatcatcag agacgcgctt ctttccaagc
2401 aaatggcaac aatgtacttg caaggaaaat tgactccgat gaattatatc
2451 tacgagaaga agactcagga agagctgcga agggaagcaa cacgcaccac
2501 tgattcattg gccaagtact gttgtgtccg tgtctcgttc tgcaaaggat
2551 ttggagaagc atacccagaa cgcccgtcaa ttcatgattg tccagtttgg
2601 attgagttga aaatcaacat tgcctacgat ttcatggatt caatctgcca
2651 gtacataacc aactgcttcg agccgctagg aatggaagat tttgcaaaat
2701 tgggaatcaa cgtcagtgat gactaaatga taactttttt cactcacccct
2751 actagatact gatttagtct tattccaaat catccaacga tatcaaactt
2801 tttcctttga actttgcata ctatgttatc acaagttcca agcagtttca
2851 atacaaacat aggatatgtt aacaactttt gataagaatc aagttaccaa
2901 ctgttcattg tgagctttga gctgtataga aggacaatgt atcccatacc
2951 tcaatcttta atagtcatca gtcactggtc ccgcaccaat tttttcgatt
3001 cgcatatgtc atatattgca ccgtggccct ttttattgta acttttaata
3051 tattttcttc ccaacttgtg aatatgattg atgaaccacc attttgagta
3101 ataaatgtat tttttgtgg

Fig. 11C (sheet 2 of 2)

1	MKLIATSLLV	PDEHTPMMSP	VNTTTKILQR	SGIKMEIPPY	LDPDSQDDDP
51	EDGVNYPDPD	LFDTKNTNMT	EYDLDVLKLG	KPAVDEARKK	IEVPDASAPP
101	NKIVEYLMYY	RTLKESELIQ	LNAYRTKRNR	LSLNLVKNNI	DREFDQKACE
151	SLVKKLKDKK	NDLQNLIDVV	LSKGTKYTGC	ITIPRTLDGR	LQVHGRKGFP
201	HVVYGKLWRF	NEMTKNETRH	VDHCKHAFEM	KSDMVCVNPY	HYEIVIGTMI
251	VGQRDHDNRD	MPPPHQRYHT	PGRQDPVDDM	SRFIPPASIR	PPPMNMHTRP
301	QPMPQQLPSV	GATFAHPLPH	QAPHNPGVSH	PYSIAPQTHY	PLNMNPIPQM
351	PQMPQMPPPL	HQGYGMNGPS	CSSENNNPFH	QNHHYNDISH	PNHYSYDCGP
401	NLYGFPTPYP	DFHHPFNQQP	HQPPQLSQNH	TSQQGSHQPG	HQGQVPNDPP
451	ISRPVLQPST	VTLDVFRRYC	RQTFGNRFFE	GESEQSGAII	RSSNKFIEEF
501	DSPICGVTVV	RPRMTDGEVL	ENIMPEDAPY	HDICKFILRL	TSESVTFSGE
551	GPEVSDLNEK	WGTIVYYEKN	LQIGEKKCSR	GNFHVDGGFI	CSENRYSLGL
601	EPNPIREPVA	FKVRKAIVDG	IRFSYKKDGS	VWLQNRMKYP	VFVTSGYLDE
651	QSGGLKKDKV	HKVYGCASIK	TFGFNVSKQI	IRDALLSKQM	ATMYLQGKLT
701	PMNYIYEKKT	QEELRREATR	TTDSLAKYCC	VRVSFCKGFG	EAYPERPSIH
751	DCPVWIELKI	NIAYDFMDSI	CQYITNCFEP	LGMEDFAKLG	INVSDD

Fig. 12A

```
  1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NVPDEHTPMM SPVNTTTKIL QRSGIKMEIP
101 PYLDPDSQDD DPEDGVNYPD PDLFDTKNTN MTEYDLDVLK LGKPAVDEAR
151 KKIEVPDASA PPNKIVEYLM YYRTLKESEL IQLNAYRTKR NRLSLNLVKN
201 NIDREFDQKA CESLVKKLKD KKNDLQNLID VVLSKGTKYT GCITIPRTLD
251 GRLQVHGRKG FPHVVYGKLW RFNEMTKNET RHVDHCKHAF EMKSDMVCVN
301 PYHYEIVIGT MIVGQRDHDN RDMPPPHQRY HTPGRQDPVD DMSRFIPPAS
351 IRPPPMNMHT RPQPMPQQLP SVGATFAHPL PHQAPHNPGV SHPYSIAPQT
401 HYPLNMNPIP QMPQMPQMPP PLHQGYGMNG PSCSSENNNP FHQNHHYNDI
451 SHPNHYSYDC GPNLYGFPTP YPDFHHPFNQ QPHQPPQLSQ NHTSQQGSHQ
501 PGHQGQVPND PPISRPVLQP STVTLDVFRR YCRQTFGNRF FEGESEQSGA
551 IIRSSNKFIE EFDSPICGVT VVRPRMTDGE VLENIMPEDA PYHDICKFIL
601 RLTSESVTFS GEGPEVSDLN EKWGTIVYYE KNLQIGEKKC SRGNFHVDGG
651 FICSENRYSL GLEPNPIREP VAFKVRKAIV DGIRFSYKKD GSVWLQNRMK
701 YPVFVTSGYL DEQSGGLKKD KVHKVYGCAS IKTFGFNVSK QIIRDALLSK
751 QMATMYLQGK LTPMNYIYEK KTQEELRREA TRTTDSLAKY CCVRVSFCKG
801 FGEAYPERPS IHDCPVWIEL KINIAYDFMD SICQYITNCF EPLGMEDFAK
851 LGINVSDD
```

Fig. 12B

```
  1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NEFKPIITLD TKPPRDANKS LAFNGGLKLI
101 TPKTEVPDEH TPMMSPVNTT TKILQRSGIK MEIPPYLDPD SQDDDPEDGV
151 NYPDPDLFDT KNTNMTEYDL DVLKLGKPAV DEARKKIEVP DASAPPNKIV
201 EYLMYYRTLK ESELIQLNAY RTKRNRLSLN LVKNNIDREF DQKACESLVK
251 KLKDKKNDLQ NLIDVVLSKG TKYTGCITIP RTLDGRLQVH GRKGFPHVVY
301 GKLWRFNEMT KNETRHVDHC KHAFEMKSDM VCVNPYHYEI VIGTMIVGQR
351 DHDNRDMPPP HQRYHTPGRQ DPVDDMSRFI PPASIRPPPM NMHTRPQPMP
401 QQLPSVGATF AHPLPHQAPH NPGVSHPYSI APQTHYPLNM NPIPQMPQMP
451 QMPPPLHQGY GMNGPSCSSE NNNPFHQNHH YNDISHPNHY SYDCGPNLYG
501 FPTPYPDFHH PFNQQPHQPP QLSQNHTSQQ GSHQPGHQGQ VPNDPPISRP
551 VLQPSTVTLD VFRRYCRQTF GNRFFEGESE QSGAIIRSSN KFIEEFDSPI
601 CGVTVVRPRM TDGEVLENIM PEDAPYHDIC KFILRLTSES VTFSGEGPEV
651 SDLNEKWGTI VYYEKNLQIG EKKCSRGNFH VDGGFICSEN RYSLGLEPNP
701 IREPVAFKVR KAIVDGIRFS YKKDGSVWLQ NRMKYPVFVT SGYLDEQSGG
751 LKKDKVHKVY GCASIKTFGF NVSKQIIRDA LLSKQMATMY LQGKLTPMNY
801 IYEKKTQEEL RREATRTTDS LAKYCCVRVS FCKGFGEAYP ERPSIHDCPV
851 WIELKINIAY DFMDSICQYI TNCFEPLGME DFAKLGINVS DD
```

Fig. 12C

tgatctttcaagccgaagcaatcaagacctcaaagccaatcaactctactcacttttcttcagaaccttaacttttgtg
tcactttccccaaaaaccgttcaagctgctgccttcactctcatcccctcctcttactccttctttctcgtccgctacta
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agatgctgacctatacgggagcaatgagcaatgtggacagctcggcggagcatcttcaaacgggtcgacagcaatgcttc
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tcgggaaaaaagacaacgaccagacggaacgcttggggaaatatgtcatatgctgaacttatcactacagccattatggc
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Fig. 13A

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Fig. 13B

MMEMLVDQGTDASSSASTSTSSVSRFGADTFMNTPDDVMMNDDMEPIPRDR
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SRFMRIQNEGAGKSSWWVINPDAKPGMNPRRTRERSNTIETTTKAQLEKSR
RGAKKRIKERALMGSLHSTLNGNSIAGSIQTISHDLYDDDSMQGAFDNVPS
SFRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDR
TDQMRIDATTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPLL
RNPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSNSSPLPGIQSCGIVA
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Fig. 14A

MQQYIYQESSATIPHHHLNQHNNPYHPMHPHHQLPHMQQLPQPLLNLNMTT
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SGMTLGMSLNLSQGGGPMPAKKKRCRKKPTDQLAQKKPNPWGEESYSDIIA
KALESAPDGRLKLNEIYQWFSDNIPYFGERSSPEEAAGWKNSIRHNLSLHS
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FRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDRT
DQMRIDATTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPLLR
NPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSNSSPLPGIQSCGIVAA
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Fig. 14B

```
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 121 cgagaacgcc catcgctgga gaccgagaat ggcaaaggat cgctgctcct ggaaaatgaa
 181 ggtgtcgcag atatcatcac tatgtgtcca ttcggagaag ttattagtgt agtatttccg
 241 tggtttcttg caaatgtgcg aacatcgcta gaaatcaagc tatcagattt caaacatcaa
 301 cttttcgaat tgattgctcc gatgaagtgg ggaacatatt ccgtaaagcc acaggattat
 361 gtgttcagac agttgaataa tttcggcgaa attgaagtta tatttaacga cgatcaaccc
 421 ctgtcgaaat tagagctcca cggcactttc ccaatgcttt ttctctacca acctgatgga
 481 ataaacaggg ataaagaatt aatgagtgat ataagtcatt gtctaggata ctcactggat
 541 aaactggaag agagcctcga tgaggaactc cgtcaatttc gtgcttctct ctgggctcgt
 601 acgaagaaaa cgtgcttgac acgtggactt gagggtacca gtcactacgc gttccccgaa
 661 gaacagtact tgtgtgttgg tgaatcgtgc ccgaaagatt tggaatcaaa agtcaaggct
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 781 gagaaaatga tgaagattca aattgaattc aatccgaacg aaactccgaa atctctgctt
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1021 gttcgccgac aatcactagt cctcaaagac tattgtcgcc caaaaccact ctacgaacca
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1921 gaactcgcat ttgtgtggac tgatcgtgag aacttttccg agctctatgt gatgcttgaa
1981 aaatggaaac cgccgagtgt ggcagccgcg ttgactttgc ttggaaaacg ttgcacggat
2041 cgtgtgattc gaaagtttgc agtggagaag ttgaatgagc agctgagccc ggtcacattc
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2281 cgccgtatct cacttctgat ggaagcttac ctccgtggaa atgaagagca catcaagatc
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2461 atggaaaata tggattctcc actggatcct gtgtacaaac tgggtgaaat gataatcgac
2521 aaagccatcg tcctaggaag tgcaaaacgt ccgttaatgc ttcactggaa gaacaaaaat
2581 ccaaagagtg acctgcacct tccgttctgt gcaatgatct tcaagaatgg agacgatctt
2641 cgccaggaca tgcttgttct tcaagttctc gaagttatgg ataacatctg gaaggctgca
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Fig. 15 (sheet 1 of 2)

2701 aacattgatt gctgtttgaa cccgtacgca gttcttccaa tgggagaaat gattggaatt
2761 attgaagttg tgcctaattg taaaacaata ttcgagattc aagttggaac aggattcatg
2821 aatacagcag ttcggagtat tgatccttcg tttatgaata agtggattcg gaaacaatgc
2881 ggaattgaag atgaaaagaa gaaaagcaaa aaggactcta cgaaaaatcc catcgaaaag
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3001 tcgtgtgttg gatattcagt tgccacgtac ataatgggaa tcaaggatcg tcacagtgat
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3121 cacggaaaga ccaaacttgg gatccagcga gatcgtcaac cgtttattct aaccgaacac
3181 tttatgacag tgattcgatc gggtaaatct gtggatggaa attcgcatga gctacaaaaa
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3301 tccttgttca ccttgatgct cggaatggag ttgcctgagc tgtcgacgaa agcggatttg
3361 gatcatttga agaaaaccct cttctgcaat ggagaaagca aagaagaagc gagaaagttt
3421 ttcgctggaa tctacgaaga agccttcaat ggatcatggt ctaccaaaac gaattggctc
3481 ttccacgcag tcaaacacta ctga

Fig. 15 (sheet 2 of 2)

```
   1 RKPWSSRSDC WTRTELRRIS QMHVNILHPQ LQTMVEQWQM RERPSLETEN GKGSLLLENE
  61 GVADIITMCP FGEVISVVFP WFLANVRTSL EIKLSDFKHQ LFELIAPMKW GTYSVKPQDY
 121 VFRQLNNFGE IEVIFNDDQP LSKLELHGTF PMLFLYQPDG INRDKELMSD ISHCLGYSLD
 181 KLEESLDEEL RQFRASLWAR TKKTCLTRGL EGTSHYAFPE EQYLCVGESC PKDLESKVKA
 241 AKLSYQMFWR KRKAEINGVC EKMMKIQIEF NPNETPKSLL HTFLYEMRKL DVYDTDDPAD
 301 EGWFLQLAGR TTFVTNPDVK LTSYDGVRSE LESYRCPGFV VRRQSLVLKD YCRPKPLYEP
 361 HYVRAHERKL ALDVLSVSID STPKQSKNSD MVMTDFRPTA SLKQVSLWDL DANLMIRPVN
 421 ISGFDFPADV DMYVRIEFSV YVGTLTLASK STTKVNAQFA KWNKEMYTFD LYMKDMPPSA
 481 VLSIRVLYGK VKLKSEEFEV GWVNMSLTDW RDELRQGQFL FHLWAPEPTA NRSRIGENGA
 541 RIGTNAAVTI EISSYGGRVR MPSQGQYTYL VKHRSTWTET LNIMGDDYES CIRDPGYKKL
 601 QMLVKKHESG IVLEEDEQRH VWMWRRYIQK QEPDLLIVLS ELAFVWTDRE NFSELYVMLE
 661 KWKPPSVAAA LTLLGKRCTD RVIRKFAVEK LNEQLSPVTF HLFILPLIQA LKYEPRAQSE
 721 VGMMLLTRAL CDYRIGHRLF WLLRAEIARL RDCDLKSEEY RRISLLMEAY LRGNEEHIKI
 781 ITRQVDMVDE LTRISTLVKG MPKDVATMKL RDELRSISHK MENMDSPLDP VYKLGEMIID
 841 KAIVLGSAKR PLMLHWKNKN PKSDLHLPFC AMIFKNGDDL RQDMLVLQVL EVMDNIWKAA
 901 NIDCCLNPYA VLPMGEMIGI IEVVPNCKTI FEIQVGTGFM NTAVRSIDPS FMNKWIRKQC
 961 GIEDEKKKSK KDSTKNPIEK KIDNTQAMKK YFESVDRFLY SCVGYSVATY IMGIKDRHSD
1021 NLMLTEDGKY VHIDFGHILG HGKTKLGIQR DRQPFILTEH FMTVIRSGKS VDGNSHELQK
1081 FKTLCVEAYE VMWNNRDLFV SLFTLMLGME LPELSTKADL DHLKKTLFCN GESKEEARKF
1141 FAGIYEEAFN GSWSTKTNWL FHAVKHY
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Fig. 16

CONVERGENT TGF-β AND INSULIN SIGNALING ACTIVATE GLUCOSE-BASED METABOLISM GENES

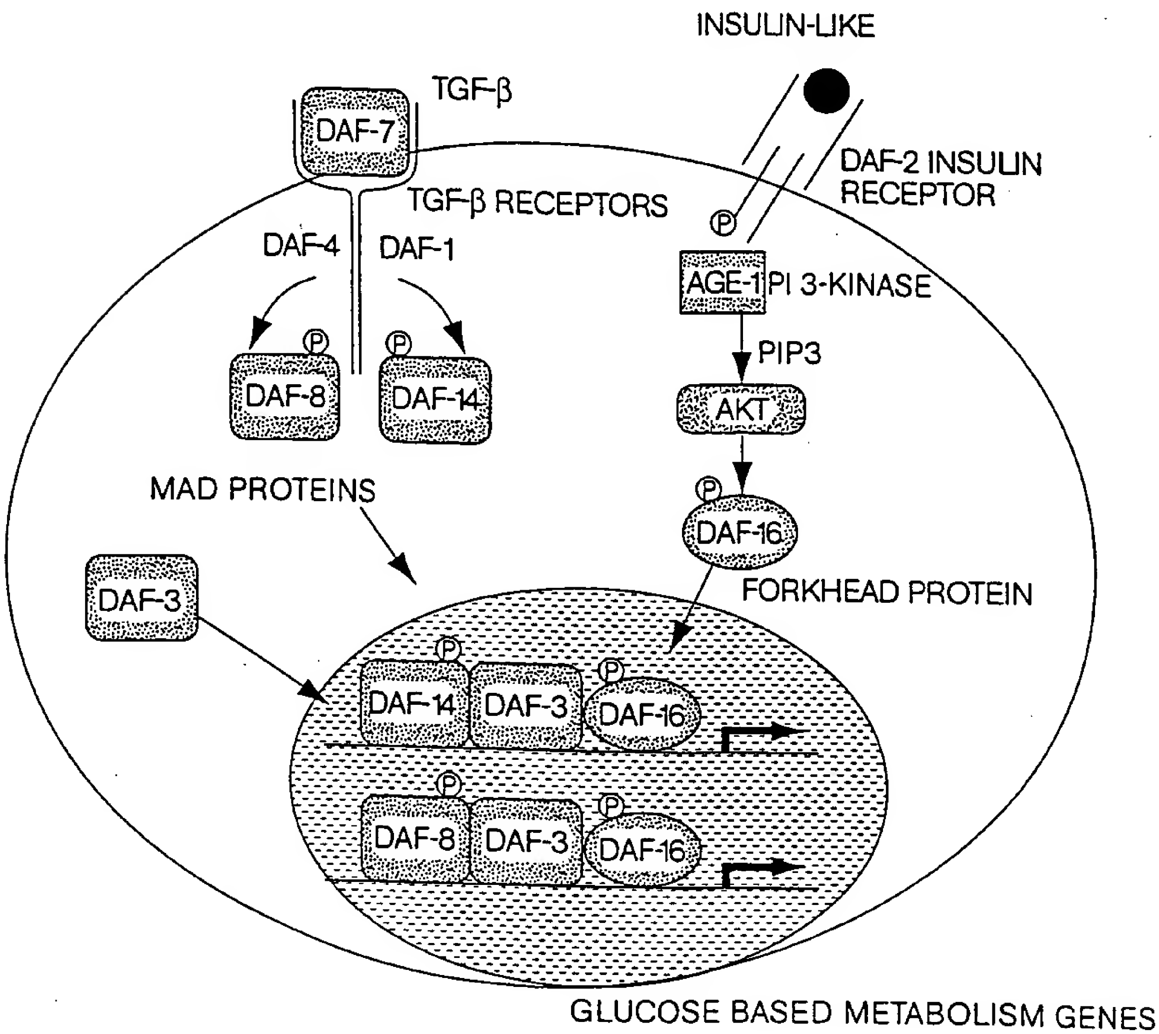


Fig. 17

IN PHEROMONE, NO TGFβ OR INSULIN-LIKE SIGNALS CAUSES REPRESSION OF ANABOLIC GENES

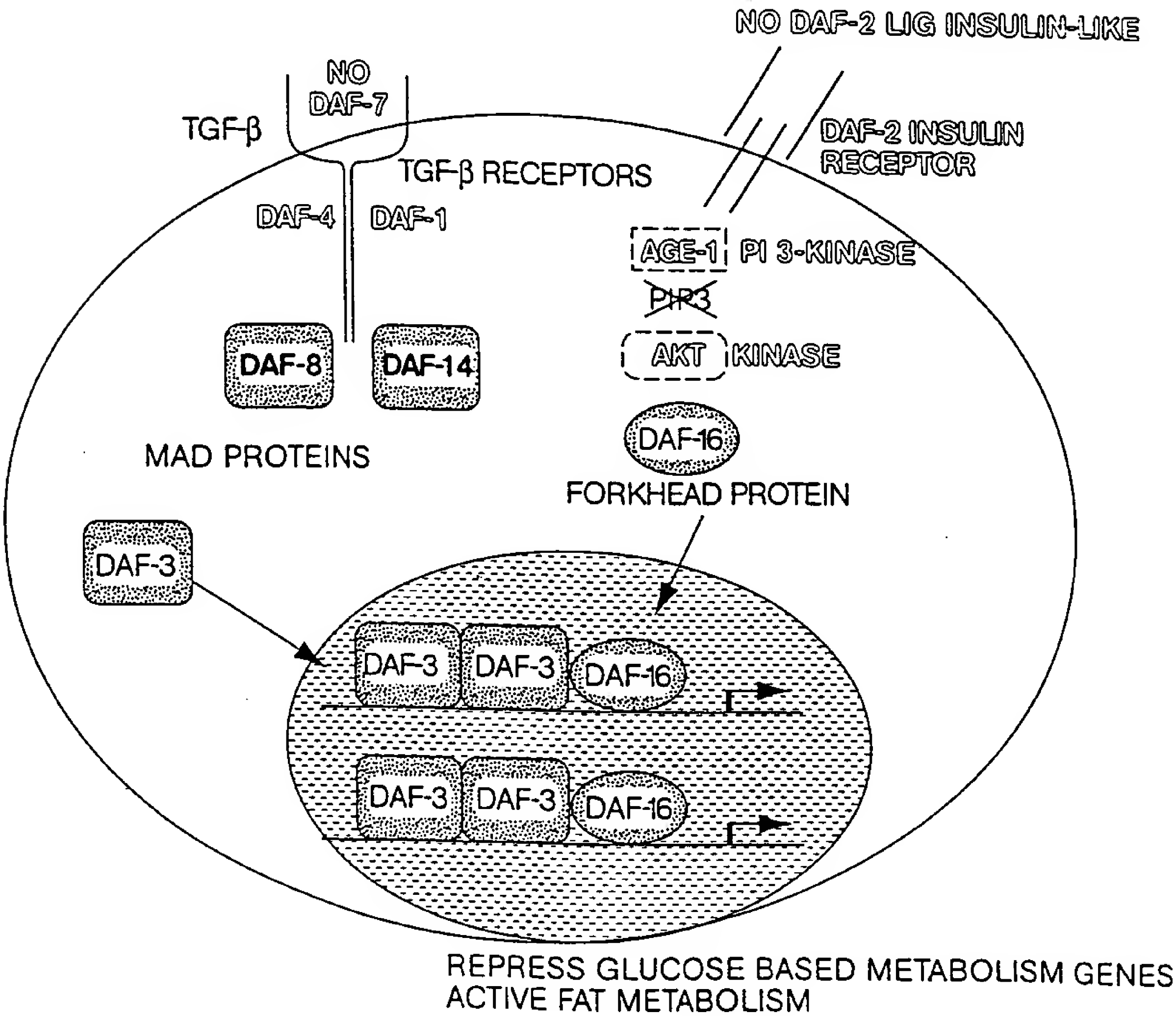
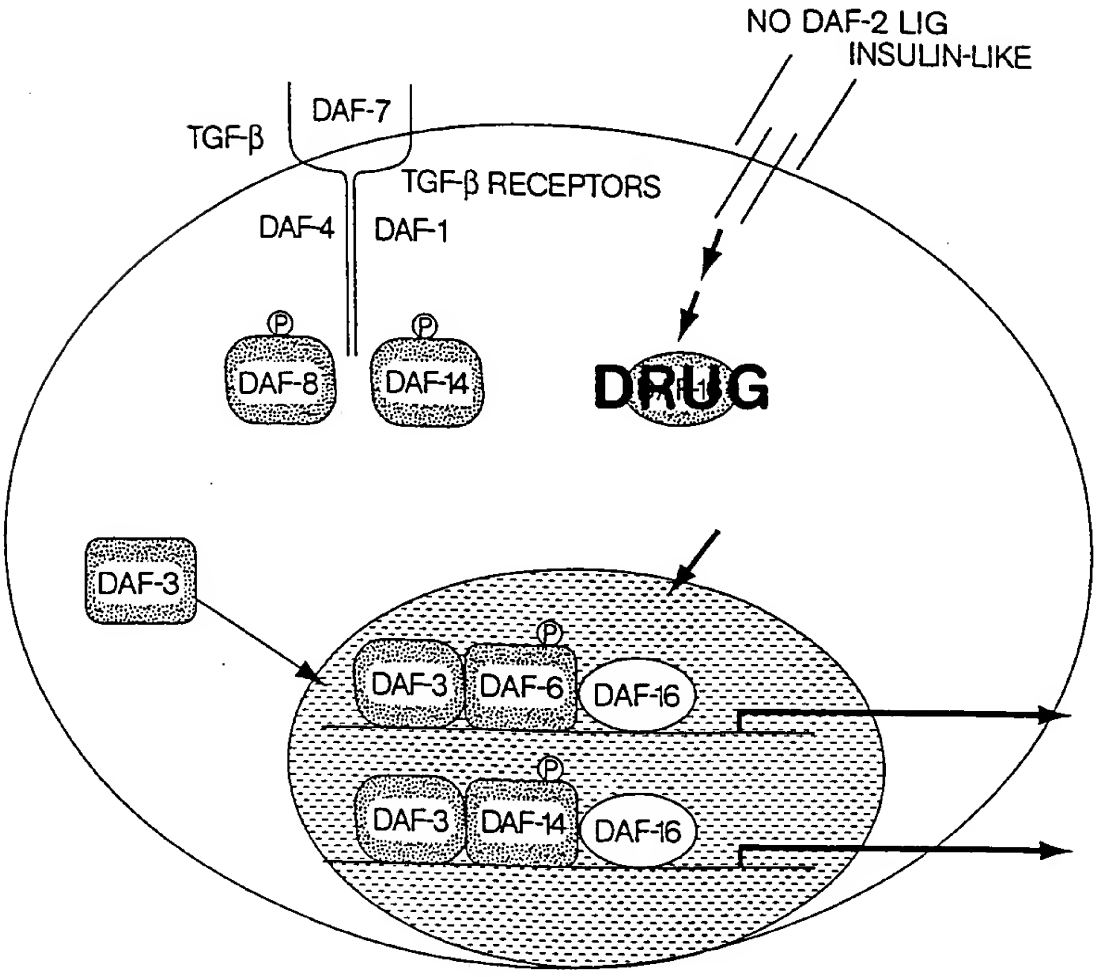


Fig. 18

**DRUGS THAT INHIBIT DAF-16 OR DAF-3
(OR PROTEINS IN THE PATHWAY)
CAN BE DISCOVERED USING REPORTER GENES
BEARING THEIR COGNATE BINDING SITES**



DRUG CAUSES A DECREASE IN DAF-16 ACTIVITY, ACTIVATING
THE REPORTER GENE LIKE A DAF-16 MUTANT.
THIS BYPASSES THE NEED FOR INSULIN

Fig. 19

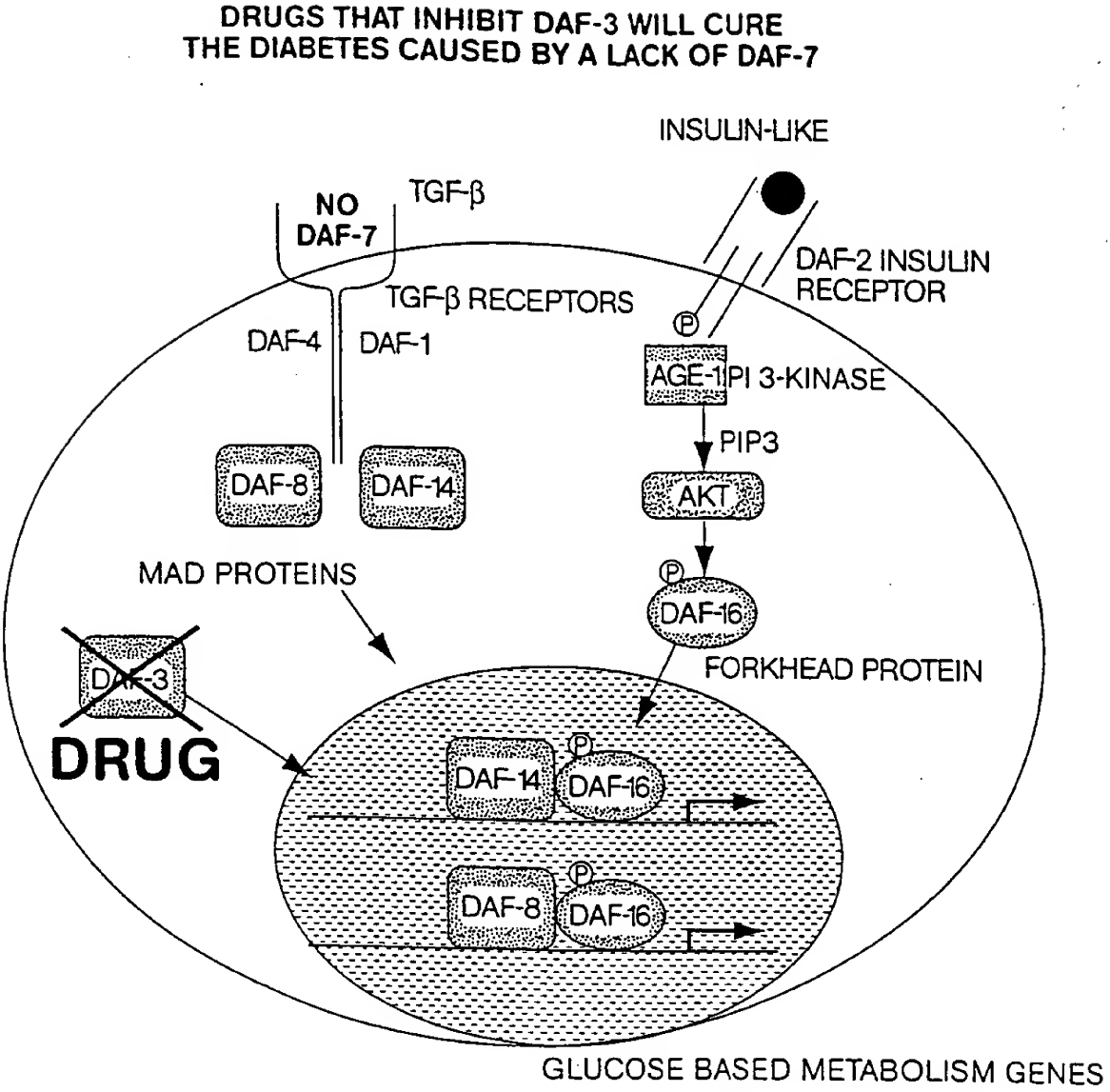


Fig. 20

```
DAF-16a1   1  -----------------------------MMEMLVDQGTDASSSASTSTSSVSRFGADTFMNTPDDVMMNDDMEPIPRDR
DAF-16b    1  -------------MNDSIDDDFPPEPRGRGYTWPMQQYIYQESSATIPHHHLNQHNNPYHPMHPHHQLPHMQQLPQPLLN
FKHR       1  ---------MAEAPQVVEIDPDFEPLPRPRSCTWPLPRPEFSQSNSATSSPAPSGSAAAN.........PDAAAGLPSASA
FKHRL1     1  MAEAPASPAPLSPLEVELDPEFEPQSRPRSCTWPLQRPELQASPAKPSGETAADSMIPE.........EEDDEDDEDGGG
AFX        1  -----------------------------------------------------------------------MRIQPQKAA

DAF-16a1  52  CN..TWPMRRPQLEPPLNSSPIIHEQIPEEDADLYGSNEQ...CGQLGGASSNGSTAMLHTPDGSNSHQTSFPSDFRMSE
DAF-16b   68  LNMTTLTSSGSSVASSIGGAQCSPCASGSSTAATNSSQQQQTVGQMLAASVPCSSSGMTLGMSLNLSQGGGPMPAKKKR
FKHR      64  AAVSADFMSNLSLLEESEDFPQAPGSVAAAVAAAAAAAATGGLCGDFQGPEAGC.LHPAPPQPPPPGPLSQHPPVPPAAA
FKHRL1    72  RAGSAMAIGGGGGSGTLGSGLLLEDS..ARVLAPGGQDPGSGPATAAGGLSGGT.QALLQPQQPLP......PPQPGAAG
AFX       10  AIIDLDPDFEPQSRPRSCTWPLPRPEIANQPSEPPEVEPDLGEKVHTEGRSEPI.LLPSRLSEPAGGP...QPGILGAVT

DAF-16a1 127  SPDDTVSGKKTTTRRNAWGNMSYAELITTAIMASPEKRLTLAQVYEWMVQNVPYFRDKGDSNSSAGWKNSIRHNLSLHSR
DAF-16b  148  CRKKP.TDQLAQKKPNPWGEESYSDIIAKALESAPDGRLKLNEIYQWFSDNIPYFGERSSPEEAAGWKNSIRHNLSLHSR
FKHR     143  GPLAGQPRKSSSSRRNAWGNLSYADLITKAIESSAEKRLTLSQIYEWMVKSVPYFKDKGDSNSSAGWKNSIRHNLSLHSK
FKHRL1   143  G..SGQPRK.CSSRRNAWGNLSYADLITRAIESSPDKRLTLSQIYEWMVRCVPYFKDKGDSNSSAGWKNSIRHNLSLHSR
AFX       86  GPRKG......GSRRNAWGNQSYAEFISQAIESAPEKRLTLAQIYEWMVRTVPYFKDKGDSNSSAGWKNSIRHNLSLHSK

DAF-16a1 207  FMRIQNEGAGKSSWWVINPDAKPGRNPRRTRERSNTIETTTKAQLEKSRRGAKKRIKERALMGSLHSTLNGNSIAGSIQT
DAF-16b  227  FMRIQNEGAGKSSWWVINPDAKPGRNPRRTRERSNTIETTTKAQLEKSRRGAKKRIKERALMGSLHSTLNGNSIAGSIQT
FKHR     223  FIRVQNEGTGKSSWWMLNPEG..GKSGKSPRRRAASMDNNSKFAKSRSRAAKKK.......AS.LQSGQEGA.GDSPGSQ
FKHRL1   220  FMRVQNEGTGKSSWWIINPDG..GKSGKAPRRRAVSMDNSNKYTKSRGRAAKKK.......AA.LQTAPESA.DDSP.SQ
AFX      160  FIKVHNEATGKSSWWMLNPEG..GKSGKAPRRRAASMDSSSKLLRGRSKAPKKK.......PSVLPAPPEGATPTSPVGH

DAF-16a1 287  ISHDLYDDDSMQGAFDNVPSSFRPRTQSNLSIPGSSSRVSPAIGSDIYDDL.EFPSWVGESVPAIPSDIVDRTDQMRIDA
DAF-16b  307  ISHDLYDDDSMQGAFDNVPSSFRPRTQSNLSIPGSSSRVSPAIGSDIYDDL.EFPSWVGESVPAIPSDIVDRTDQMRIDA
FKHR     292  FSKWPASPGSHSNDDFDNWSTFRPRTSSNAS..TISGRLSPIM..TEQDDLGEGD..VHSMVYPPSAAKMAST.......
FKHRL1   288  LSKWPGSPTSRSSDELDAWTDFRSRTNSNAS..TVSGRLSPIMASTELDEVQDDDAPLSPMLYSSSASLSPSVSKPCTVE
AFX      231  FAKWSGSPCSRNREEADMWTTFRPRSSSNAS..SVSTRLSPLRPESEV.LAEEIPASVSSYAGGVPPTLNEGLELLDGLN

DAF-16a1 366  TTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPLLRNPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSN
DAF-16b  386  TTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPLLRNPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSN
FKHR     359  LPSLSEISNPENM.ENLLDNL.NLLSSPTSLTVSTQSSPGTMMQQTPCYSFAPP.NTSLNSPSPNYQKYTYGQSSMSPLP
FKHRL1   366  LPRLTDMAGTMNLNDGLTENLMDDLLDNITLPPSQPSPTGGLMQRSSSFPYTTK.GSGLGSPTSSFNSTVFGPSSLNSLR
AFX      308  LTSSHSLLSRSGLSGFSLQHPGVTGPLHTYSSSLFSPAEGPLSAGEGCFSSSQALEALLTSDTPPPPADVLMTQVDPILS

DAF-16a1 446  SSPLPGIQS..CGIVAAQHTVASSSALPIDLENLTLPDQPLMDTMDVDALIRHELSQAGGQHIHFDL-------------
DAF-16b  466  SSPLPGIQS..CGIVAAQHTVASSSALPIDLENLTLPDQPLMDTMDVDALIRHELSQAGGQHIHFDL-------------
FKHR     436  QMPIQTLQDNK.SSYGGMSQYNCAPGLLKELLTSDSPPHNDI.MTPVDPGVAQPNSRVLGQNV...MMGPNSVMSTYGSQ
FKHRL1   445  QSPMQTIQENKPATFSSMSHY..GNQTLQDLLTSDSLSHSDVMMTQSDPLMSQASTAVSAQNSRRNVMLRNDPMMSFAAQ
AFX      388  QAPTLLLLGGLPSS....SKLATGVGLCPKPLEARGPSSLVPTLSMIAPPPVMASAPIPKALGTPVLTPPTEAASQDRMP

DAF-16a1 511  --------------------------------------------------------------------------------
DAF-16b  531  --------------------------------------------------------------------------------
FKHR     511  ASHNKMMNPSSH.THPGHAQQTSAVNGRPLPHTVSTMPHTSGMNRLTQVKTPVQVPLPHPMQMSALGGYSSVSSCNGYGR
FKHRL1   523  PNQGSLVN.QNL.LHHQHQTQGALGGSRALSNSVSNM.GLSESSSLGSAKHQQQSPVSQSMQ.TLSDSLSGSSLYSTSAN
AFX      464  QDLDLDMYMENLECDMDNIISDLMDEGEGLDFNFEPDP------------------------------------------
```

FIG. 21A-1

DAF-16a1	511	~~~~~~
DAF-16b	531	~~~~~~
FKHR	590	MGLLHQEKLPSDLD.GMFIERLDCDMESIIRNDLMDGDTLDFNFDNVLPNQ........SFPHSVKTTTHSWVSG
FKHRL1	599	LPVMGHEKFPSDLDLDMFNGSLECDMESIIRSELMDADGLDFNFDSLISTQNVVGLNVGNFTGAKQASSQSWVPG
AFX	502	~~~~~~

FIG. 21A-2

Fork head Domain Alignment (*C. elegans*, human, others)

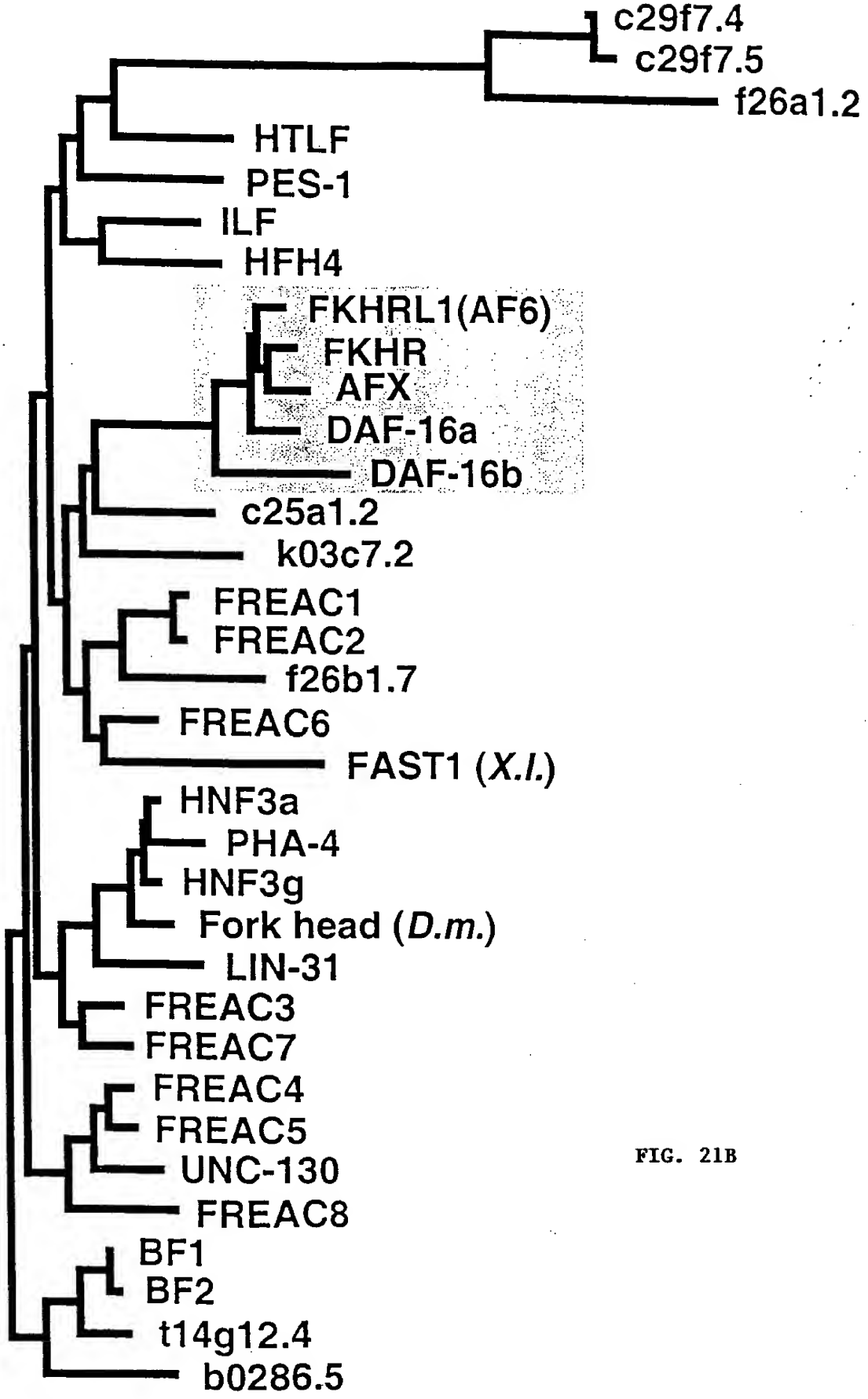


FIG. 21B

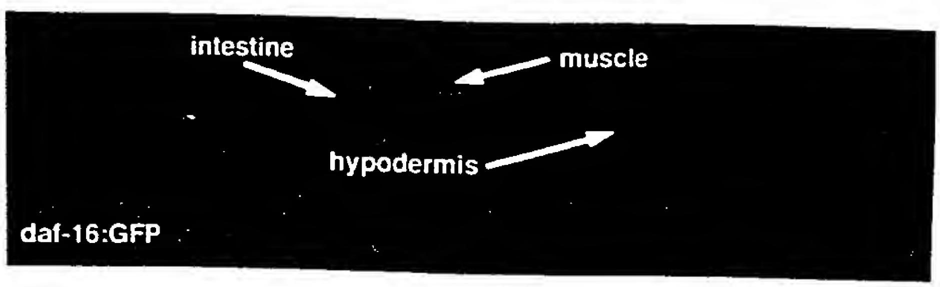
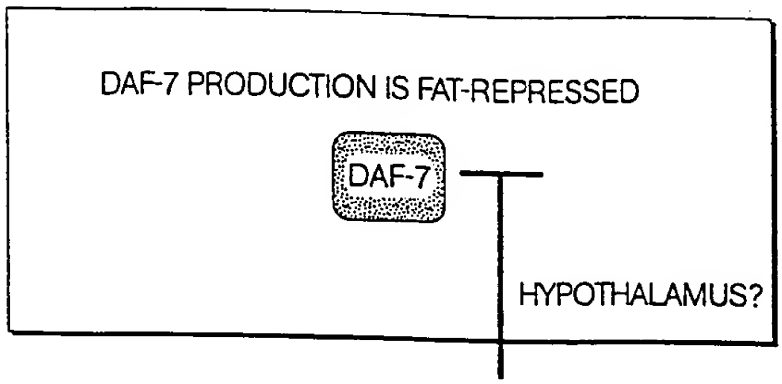


Fig. 22

INJECTION OF OF DAF-7 BYPASSES OBESITY-INDUCED DEFECTS IN INSULIN-REGULATION OF METABOLISM



FATTY ACIDS IN BLOOD REPRESS DAF-7 IN ANALOGY TO PHEROMONE REGULATION OF DAF-7 IN C. ELEGANS

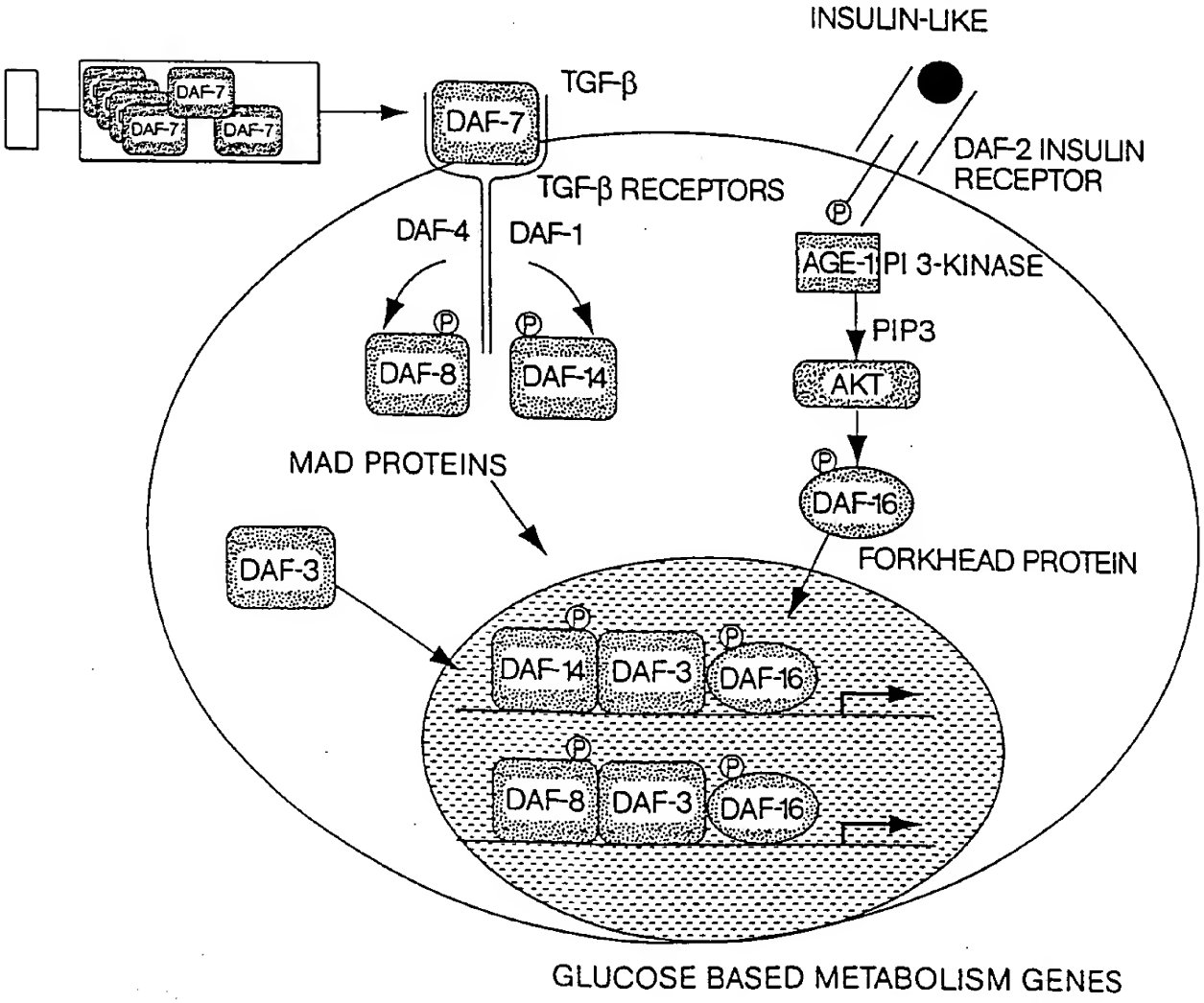


Fig. 23

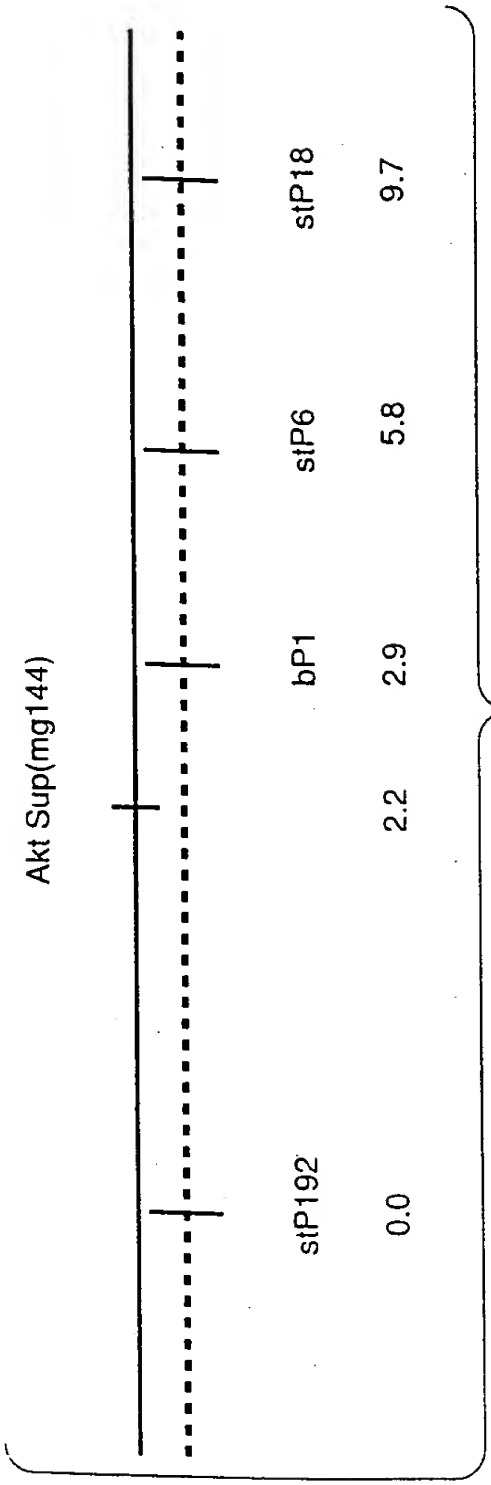


Fig. 24

Comparison of the human AKT protein sequence to the cosmid sequence C12D8, located in the genetic interval where sup(mg144) maps. Numbering in the AKT protein sequence by amino acid residues, and in the cosmid sequence by nucleotide position.

```
 Score = 450 (207.4 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 79/121 (65%), Positives = 97/121 (80%), Frame = +1

Query:    319 EVLEDNDYGRAVDWWGLGVVMYEMMCGRLPFYNQDHEKLFELILMEEIRFPRTLGPEAKS 378
              +VL+D+DYGR VDWWG+GVVMYEMMCGRLPFY++DH KLFELI+  ++RFP  L  EA++
Sbjct:  33685 QVLDDHDYGRCVDWWGVGVVMYEMMCGRLPFYSKDHNKLFELIMAGDLRFPSKLSQEART 33864

Query:    379 LLSGLLKKDPTQRLGGGSEDAKEIMQHRFFANIVWQDVYEKKLSPPFKPQVTSETDTRYFD 439
              LL+GLL KDPTQRLGGG EDA EI +  FF  + W+  Y K++ PP+KP V SETDT YFD
Sbjct:  33865 LLTGLLVKDPTQRLGGGPEDALEICRADFFRTVDWEATYRKEIEPPYKPNVQSETDTSYFD 34047

 Score = 256 (118.0 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 48/66 (72%), Positives = 59/66 (89%), Frame = +1

Query:    146 TMNEFEYLKLLGKGTFGKVILVKEKATGRYYAMKILKKEVIVAKDEVAHTLTENRVLQNS 205
              TM +F++LK+LGKGTFGKVIL KEK T + YA+KILKK+VI+A++EVAHTLTENRVLQ
Sbjct:  32314 TMEDFDFLKVLGKGTFGKVILCKEKRTQKLYAIKILKKDVIIAREEVAHTLTENRVLQRC 32493

Query:    206 RHPFLT 211
              +HPFLT
Sbjct:  32494 KHPFLT 32511

 Score = 190 (87.6 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 36/45 (80%), Positives = 37/45 (82%), Frame = +2

Query:    276 KLENLMLDKDGHIKITDFGLCKEGIKDGATMKTFCGTPEYLAPEV 320
              KLENL+LDKDGHIKI DFGLCKE I  G    TFCGTPEYLAPEV
Sbjct:  33509 KLENLLLDKDGHIKIADFGLCKEEISFGDKTSTFCGTPEYLAPEV 33643

 Score = 188 (86.7 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 37/57 (64%), Positives = 42/57 (73%), Frame = +3

Query:    209 FLTALKYSFQTHDRLCFVMEYANGGELFFHLSRERVFSEDRARFYGAEIVSALDYLH 265
              +  LKYSFQ   LCFVM++ANGGELF H+ +  FSE RARFYGAEIV AL YLH
Sbjct:  32667 YFQELKYSFQEQHYLCFVMQFANGGELFTHVRKCGTFSEPRARFYGAEIVLALGYLH 32837

 Score = 166 (76.5 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 29/59 (49%), Positives = 42/59 (71%), Frame = +1

Query:     53 NNFSVAQCQLMKTERPRPNTFIIRCLQWTTVIERTFHVETPEEREEWATAIQTVADGLK 111
              + F++   Q M  E+PRPN F++RCLQWTTVIERTF+ E+ E R+ W  AI++++   K
Sbjct:  31846 STFAIFYFQTMLFEKPRPNMFMVRCLQWTTVIERTFYAESAEVRQRWIHAIESISKKYK 32022

 Score = 134 (61.8 bits), Expect = 5.2e-167, Sum P(8) = 5.2e-167
 Identities = 24/33 (72%), Positives = 30/33 (90%), Frame = +3

Query:    210 LTALKYSFQTHDRLCFVMEYANGGELFFHLSRE 242
              L  LKYSFQT+DRLCFVME+A GG+L++HL+RE
Sbjct:  33156 LQELKYSFQTNDRLCFVMEFAIGGDLYYHLNRE 33254
```

Fig. 25

Fig. 26A

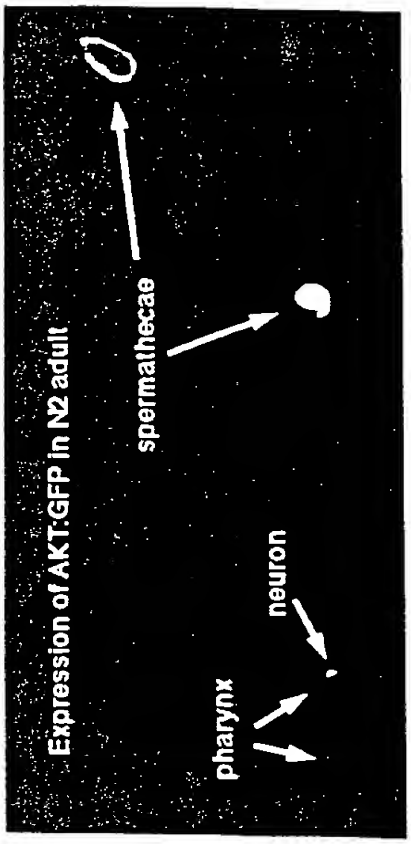
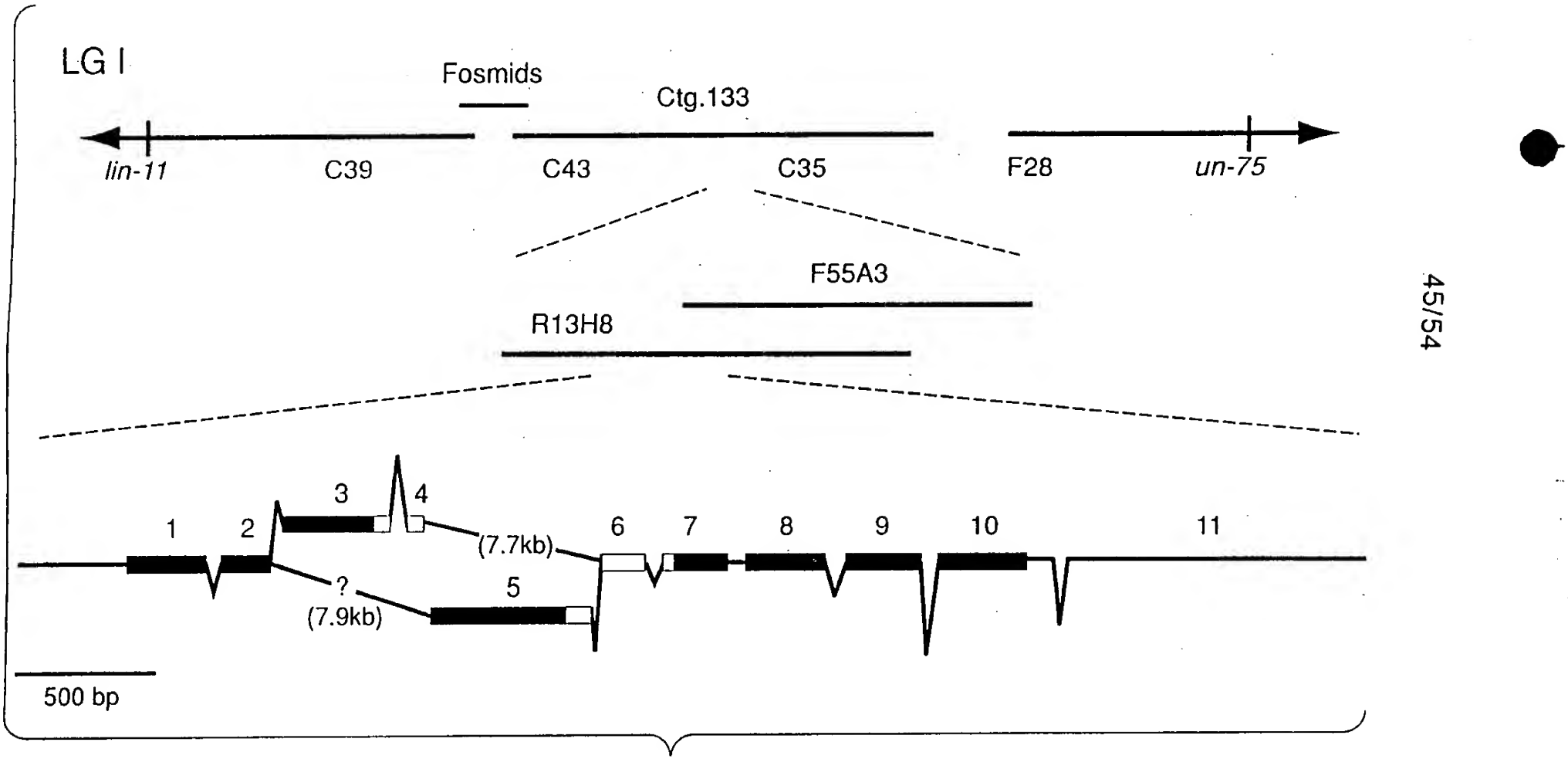


Fig. 26B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Ctg.133
lin-11
C39
C43
C35
F28
un-75
F55A3
R13H8
1
2
3
4
(7.7kb)
6
7
8
9
10
11
?
(7.9kb)
5
500 bp

Fig. 27

```
               1             15 16            30 31            45 46            60
1 ZK84.6       -MNSVFTIIFVLCAL QVAASFRQSFG---P SMSEESASMQLLREL QH--NMMESAHRPMP  54
2 ZK75.1       -MFSFFT-YFLLSAL LLSASCRQ------P SMDT-SKADRILREI E----METELENQLS  47
3 ZK1251.2     ----MPPIILVFFLV LIPASQQY------P FSLE-SLNDQIINEE VI--EYMLENSIRSS  47
4 C06E2        --MIVTLIVFLVIGL QMAHLSQVSGNNENG FLNP-FDLSQWSEEI LHRQYHHHHHHHHGN  57
5 ZK75.2       ----MNAIIFCLLFT TVTATYEVF-----G KGIEHRNEHLIINQL D---IIPVESTPTPN  48
6 ZK75.3       MKLSVVLALFIIFQL GAASLMRN------W MFDFEKELEHDYDDS E---IGFHNIHSLMA  51
7 C17C3        --------------- --------------- ---------MKLLHI F---IIFLLFQSCSN  18
8 F13B12       --------------- --------------- ----MYWFRQVYRPS FF--FGFLAILLLSS  50
9 INSULIN      --------------- --------------- -------------MA LWMRLLPLLALLALW  17
CONSENSUS      --------------- --------------- --------------- ---------------

               61            75 76            90 91           105 106          120
1 ZK84.6       RARRVPAPGETRACG RKLISLVMAVCGD-L CN------------- ---------------  85
2 ZK75.1       RARRVPA-GEVRACG RRLLLFVWSTCGE-P CT------------- ---------------  77
3 ZK1251.2     RTRRVPDEKKIYRCG RRIHSYVFAVCGK-A CE------------- ---------------  78
4 C06E2        RARRTLETEKIYRCG RKLYTDVLSACNG-P CE------------- ---------------  88
5 ZK75.2       RASRVQK----RLCG RRLILFMLATCG--E CD------------- ---------------  74
6 ZK75.3       RSRRGDK---VKICG TKVLKMVMVMCGG-E CS------------- ---------------  79
7 C17C3        KMCQYSK-KKYKICG VRALKHMKVYCTR-G MT------------- ---------------  48
8 F13B12       PTPSDAS---IRLCG SRLTTTLLAVCRNQL CTGLTAFKRSADQSY APTTRDLFHIHHQQ-  80
9 INSULIN      GPDPAAAFVNQHLCG SHLVEALYLVCGERG FFYTPKTRREAEDLQ VGQVELGGGPGAGSL  77
CONSENSUS      -------------CG -----------C--- --------------- ---------------
                         B CHAIN                            C PEPTIDE

               121          135 136          150 151          165 166          180
1 ZK84.6       -------PQEGKDIA TECCGNQCSDDYIRS ACCP-----       112
2 ZK75.1       -------PQEDMDIA TVCCTTQCTPSYIKQ ACCPEK---       106
3 ZK1251.2     -------SNTEVNIA SKCCREECTDDFIRK QCCP-----       105
4 C06E2        -------PGTEQDLS KLCCGNQCTFVEIRK ACCADKL--       118
5 ZK75.2       -------TDSSEDLS HICCIKQCDVQDIIR VCCPNSFRK       106
6 ZK75.3       -------S-TNENIA TECCEKMCTMEDITT KCCPSR---       107
7 C17C3        -------R-DYGKLL VTCCSKGCNAIDIQR ICL------        73
8 F13B12       ---------KRGGIA TECCEKRCSFAYLKT FCCNQDDN-       109
9 INSULIN      QPLALEGSLQKRGIV EQCCTSICSLYQLEN YCN-------      110
CONSENSUS      -----------------CC---C------- --C-------
                         A CHAIN
```

Fig. 28

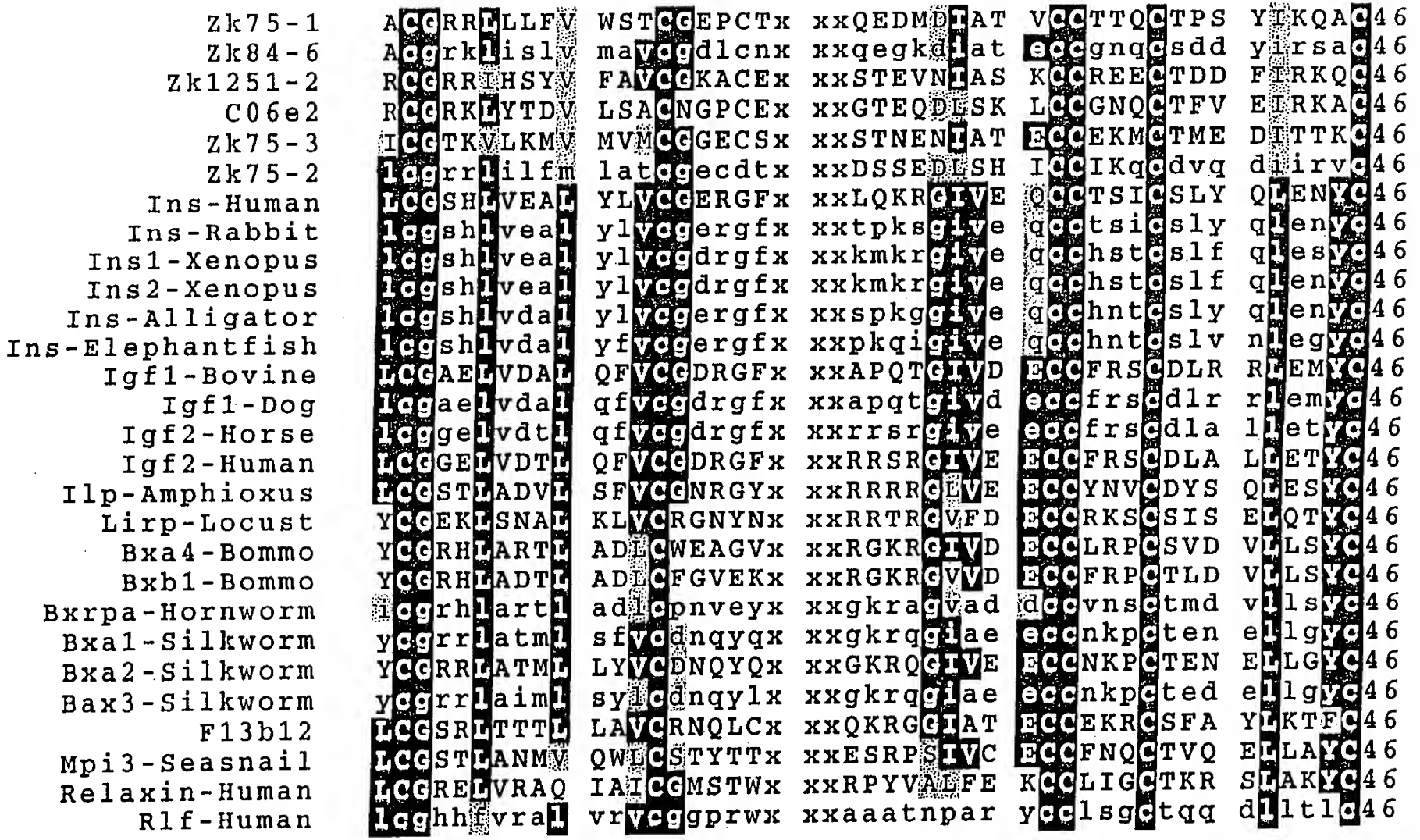
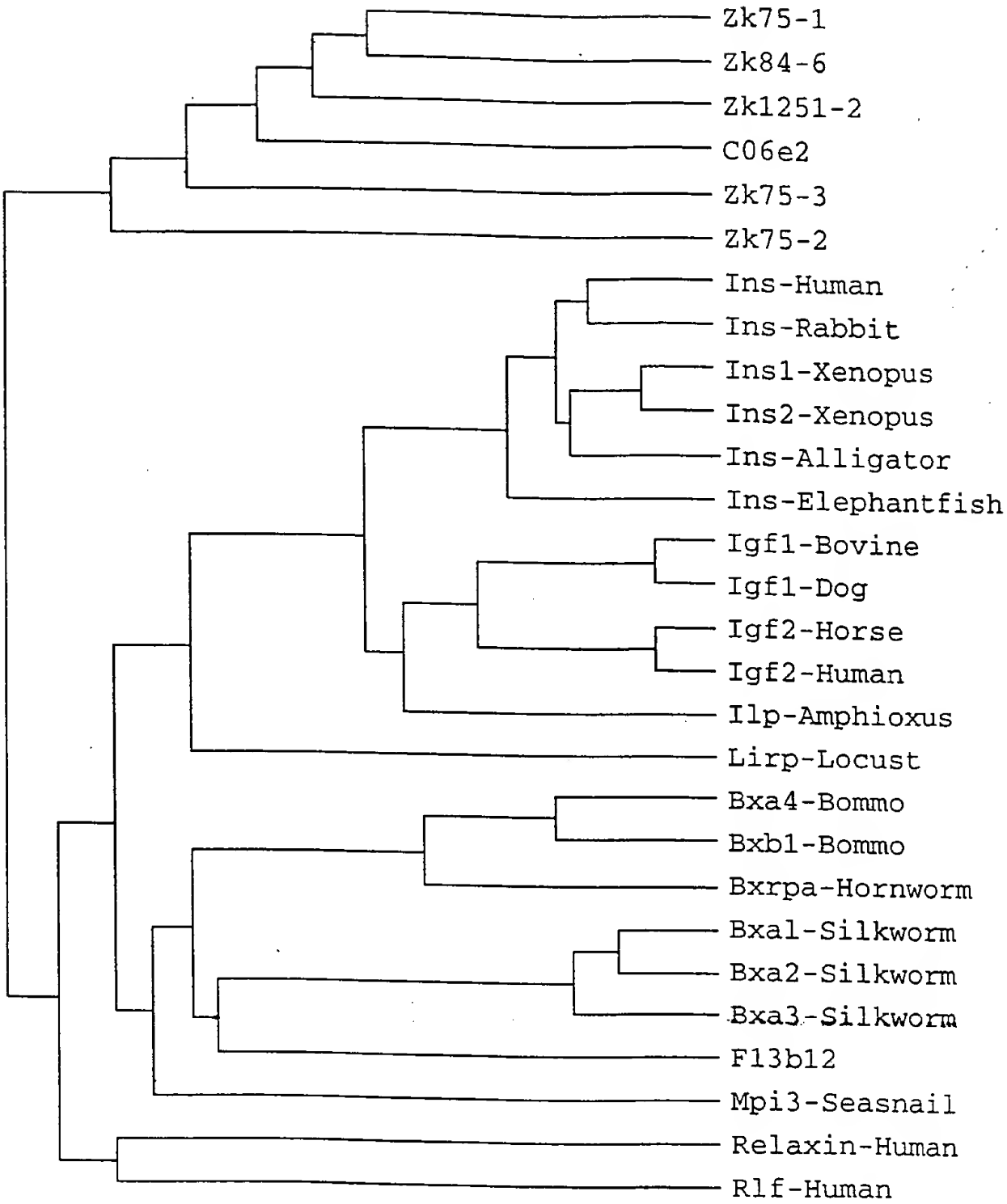

Zk75-1 ACGRRLLLFV WSTCGEPCTx xxQEDMDIAT VCCTTQCTPS YIKQACx46
Zk84-6 Agrklislv mavcgdlcnx xxqegkdiat ecgnqcsdd yirsacx46
Zk1251-2 RCGRRIHSYV FAVCGKACEx xxSTEVNIAS KCCREECTDD FIRKQCx46
C06e2 RCGRKLYTDV LSACNGPCEx xxGTEQDLSK LCCGNQCTFV EIRKACx46
Zk75-3 ICGTKVLKMV MVMCGGECSx xxSTNENIAT ECCEKMCTME DITTKCx46
Zk75-2 lagrrlilfm latcgecdtx xxDSSEDLSH ICCIKqcdvq diirvcx46
Ins-Human LCGSHLVEAL YLVCGERGFx xxLQKRGIVE QCCTSICSLY QLENYCx46
Ins-Rabbit lcgshlveal ylvcgergfx xxtpksgive qcctsicsly qlenycx46
Ins1-Xenopus lcgshlveal ylvcgdrgfx xxkmkrgive qcchstcslf qlesycx46
Ins2-Xenopus lcgshlveal ylvcgdrgfx xxkmkrgive qcchstcslf qlenycx46
Ins-Alligator lcgshlvdal ylvcgergfx xxspkggive qcchntcsly qlenycx46
Ins-Elephantfish lcgshlvdal yfvcgergfx xxpkqigive qcchntcslv nlegycx46
Igf1-Bovine LCGAELVDAL QFVCGDRGFx xxAPQTGIVD ECCFRSCDLR RLEMYCx46
Igf1-Dog lcgaelvdal qfvcgdrgfx xxapqtgivd eccfrscdlr rlemycx46
Igf2-Horse lcggelvdtl qfvcgdrgfx xxrrsrgive eccfrscdla lletycx46
Igf2-Human LCGGELVDTL QFVCGDRGFx xxRRSRGIVE ECCFRSCDLA LLETYCx46
Ilp-Amphioxus LCGSTLADVL SFVCGNRGYx xxRRRRGLVE ECCYNVCDYS QLESYCx46
Lirp-Locust YCGEKLSNAL KLVCRGNYNx xxRRTRGVFD ECCRKSCSIS ELQTYCx46
Bxa4-Bommo YCGRHLARTL ADLCWEAGVx xxRGKRGIVD ECCLRPCSVD VLLSYCx46
Bxb1-Bommo YCGRHLADTL ADLCFGVEKx xxRGKRGVVD ECCFRPCTLD VLLSYCx46
Bxrpa-Hornworm iagrhlartl adlcpnveyx xxgkragvad dccvnsctmd vllsycx46
Bxa1-Silkworm yagrrlatml sfvcdnqyqx xxgkrqgiae eccnkpcten ellgycx46
Bxa2-Silkworm YCGRRLATML LYVCDNQYQx xxGKRQGIVE ECCNKPCTEN ELLGYCx46
Bax3-Silkworm yagrrlaiml sylcdnqylx xxgkrqgiae eccnkpcted ellgycx46
F13b12 LCGSRLTTTL LAVCRNQLCx xxQKRGGIAT ECCEKRCSFA YLKTFCx46
Mpi3-Seasnail LCGSTLANMV QWLCSTYTTx xxESRPSIVC ECCFNQCTVQ ELLAYCx46
Relaxin-Human LCGRELVRAQ IAICGMSTWx xxRPYVALFE KCCLIGCTKR SLAKYCx46
R1f-Human lcghhfvral vrvcggprwx xxaaatnpar ycclsgctqq dlltlcx46

Fig. 29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Ins2-Xenopus
Ins-Alligator
Ins-Elephantfish
Igf1-Bovine
Igf1-Dog
Igf2-Horse
Igf2-Human
Ilp-Amphioxus
Lirp-Locust
Bxa4-Bommo
Bxb1-Bommo
Bxrpa-Hornworm
Bxa1-Silkworm
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Bxa3-Silkworm
F13b12
Mpi3-Seasnail
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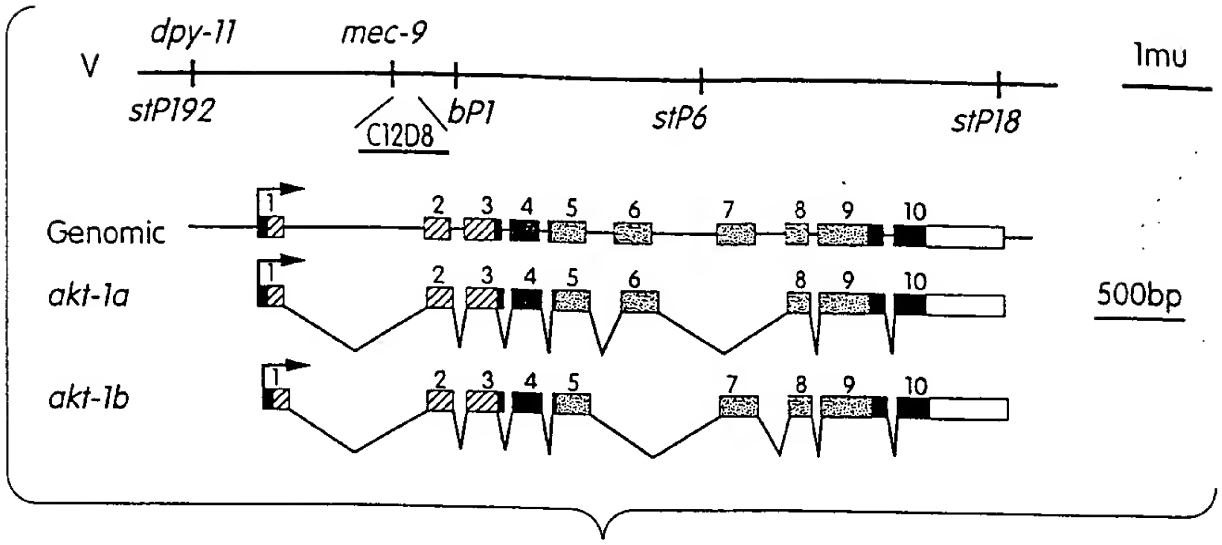
Rlf-Human

Fig. 30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500bp

Fig. 31

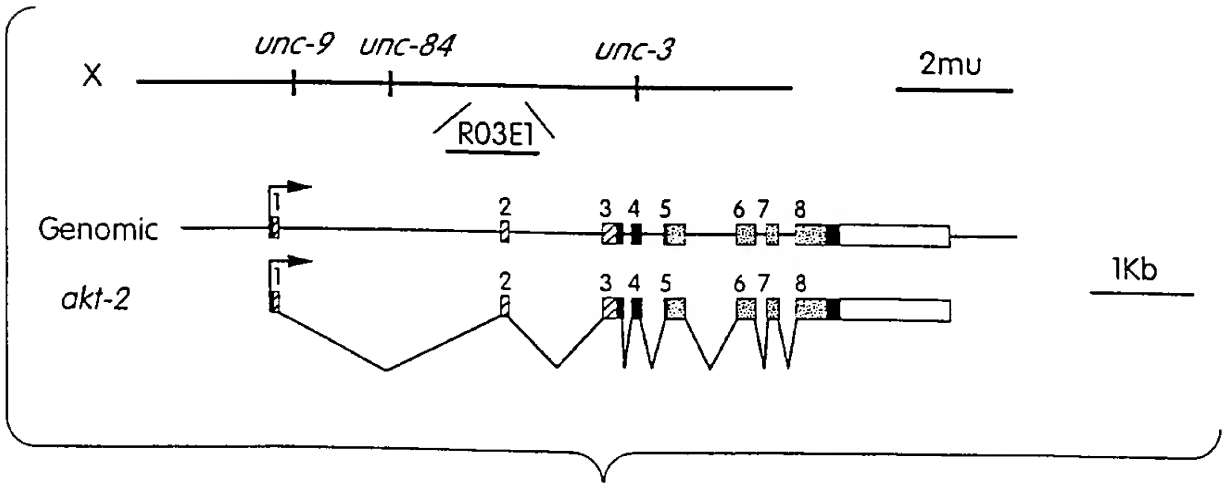
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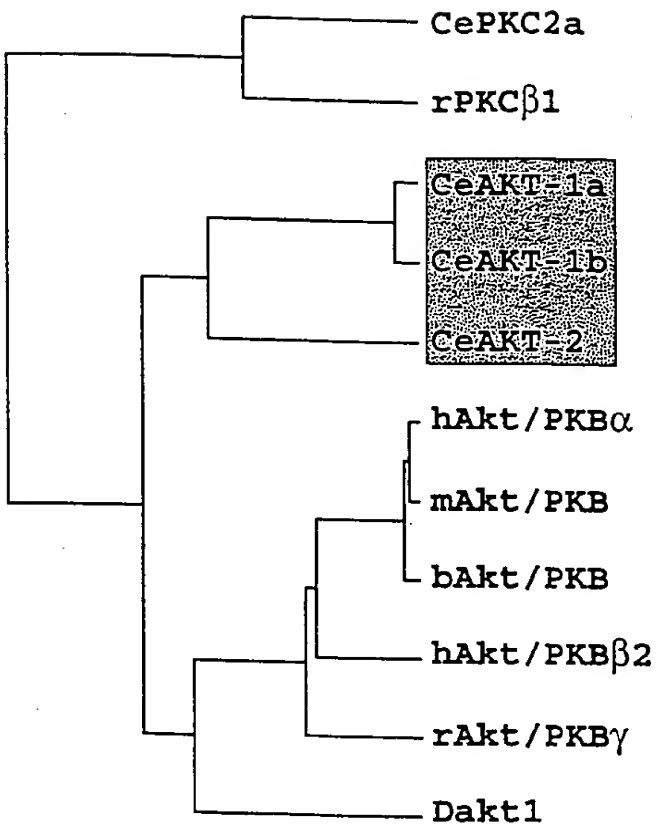
Fig. 32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rPKCβ1
CeAKT-1a
CeAKT-1b
CeAKT-2
hAkt/PKBα
mAkt/PKB
bAkt/PKB
hAkt/PKBβ2
rAkt/PKBγ
Dakt1

Fig. 33

AKT-1a	MSMTSLSTKSRR--QEDVVIEGWLHKKGEHIRNWRPRYFMIFNDGALLGFRAKPKEGQPFPEPL
AKT-1b	.............--...
AKT-2	M..ENAHLQK..I..S..........IL.R..T.....S....D..L
hAkt/PKBa	MSDVAI.K.......R..Y.KT.......LLK...TFI.YKER.QDVDQREA
AKT-1a	NDFMIKDAATMLFEKPRPNMFMVRCLQWTTVIERTFYAESAEVRQRWIHAIESIS--KKYKGTN
AKT-1b	....--.......
AKT-2	.N...R....VCLD.........I...............D..DF.....E..QAV.SHNRL.ENA
hAkt/PKBa	.N.SVAQCQL.KT.R.....T.II..........HV.TP.E.EE.TT..QTVADGL.KQE--
	mg144 T
AKT-1a	ANPQEELMETNQQPKIDEDSEFAGAAHAIMGQPSSGHGDNCSIDFRASMISIADTSEAAKRDKI
AKT-1b	....
AKT-2	G.TSMQEED..GN.SGES.VNM---------DAT.TRS..---..ESTVMN.DEPE.VPRKNTV
hAkt/PKBa	----------------E.EMD.-----------R.GSPS..SGAE--------EMEV.L.KPKHRV
AKT-1a	TMEDFDFLKVLGKGTFGKVILCKEKRTQKLYAIKILKKDVIIAREEVAHTLTENRVLQRCKHPF
AKT-1b	....
AKT-2	..D........Q.........R..SSD.......IR.EMVVD.S...............YA.V.
hAkt/PKBa	..NE.EY..L.........V....A.GRY..M......E...V.KD..............NSR..
AKT-1a	LTELKYSFQEQHYLCFVMQFANGGELFTHVRK----CGTFSEPRARFYGAEIVLALGYLH-RC
AKT-1b	.........TNDR.....E..I..D.YY.LNREVQMNKEG.........S..........-..
AKT-2	..L.......A.YHL....E..........LQR----K....A.T....S..........-AN
hAkt/PKBa	..A.......THDR.....EY.......F.LSRE----RV...D.........S..I....-HR
	....S..D.....SEK
AKT-1a	DIVYRDMKLENLLLDKDGHIKIADFGLCKEEISFGDKTSTFCGTPEYLAPEVLDDHDYGRCVDW
AKT-1b	S.....L...
AKT-2	N...............R.......T...........KY...................IE.I..D.S
hAkt/PKBa	NV....L.....M............T.......G.KD.ATMK...............E.N....A
AKT-1a	WGVGVVMYEMMCGRLPFYSKDHNKLFELIMAGDLRFPSKLSQEARTLLTGLLVKDPTQRLGGGP
AKT-1b	....
AKT-2	...............SA.ENG......TTC..K..NR..P...V....S...ERV.AK....A.
hAkt/PKBa	...L...........NQ..E.......LMEEI....RT.GP..KS...S.....K....K.....S
AKT-1a	EDALEICRADFFRTVDWEATYRKEIEPPYKPNVQSETDTSYFDN-EFTSQPVQLTPPSRSGALA
AKT-1b	....-...................
AKT-2	D..R.VS...E..KD......L...V...F....M......F..RVRYV.ILLKV-----.E.I
hAkt/PKBa	...K..MQHR...AGIV.QHV.E.KLS..F..Q.T.....R...E-...A.MITI...DQDDSME
AKT-1a	TVDEQEEMQSNFTQFSFHNVMGSINRIHEASEDNEDYDMGZ
AKT-1b	....
AKT-2	
hAkt/PKBa	C..--S.RRPH.P...YSASSTA

Fig. 34

cataaaaatccagtaaatggtaaaattttcaatttcagatccatctcgatggaggatctcacaccaactaacacgtcgctcgacaccacaactac
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Fig. 35A

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TCACAGCCATCAACGTGAGTTTGAAGCATTTTTTTCTTGCATTAAAAGTTTTACCTTGCACTGACCAAAATTTATTGAAACTATTAATTATTTGA
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TTTGTAGGAAATGATGCGTGAACAGAAGGCGCTGCGCCGCAAACAAGAAAAGGAGGAGAAAAAGGCGCTAAAAGCCGAGCAAGTGAGCAAGAAGC
TTTCAATGCAAATGGACAAGAAGTCGCCTTGAAGGCTCACCTCCCTTCTACTCCCCACAAAATCACCATCAAACAAATCACACTTTTGTATCATT
TTGCGTCC

Fig. 35B

MEDLTPTNTSLDTTTTNNDTTSDREAAPTTLNLTPTASESENSLSPVTAEDLIAKSIKEGCPKRTSNDFMFLQSMGEG
AYSQVFRCREVATDAMFAVKVLQKSYLNRHQKMDAIIREKNILTYLSQECGGHPFVTQLYTHFHDQARIYFVIGLV
ENGDLGESLCHFGSFDMLTSKFFASEILTGLQFLHDNKIVHRDMKPDNVLIQKDGHILITDFGSAQAFGGLQLSQEGFT
DANQASSRSSDSGSPPPTRFYSDEEEENTARRTTFVGTALYVSPEMLADGDVGPQTDIWGLGCILFQCLAGQPPFRAV
NQYHLLKRIQELDFSFPEGFPEEASEIIAKILVRDPSTRITSQELMAHKFFENVDWVNIANIKPPVLHAYIPATFGEP
EYYSNIGPVEPGLDDRALFRLMNLGNDASASQPSTPSNVEHRGDPFVSEIAPRANSEAEKNRAARAQKLEEQRVK
NPFHIFTNNSLILKQGYLEKKRGLFARRRMFLLTEGPHLLYIDVPNLVLKGEVPWTPCMQVELKNSGTFFIHTPNR
VYYLFDLEKKADEWCKAINDVRKRYSVTIEKTFNSAMRDGTFGSIYGKKKSRKEMMREQKALRRKQEKEEKKAL
KAEQVSKKLSMQMDKKSP

Fig. 36

MEDLTPTNTSLDTTTTNNDTTSDREAAPTTLNLTPTASESENSLSPVTAEDLIAKSIKEGCPKRTSNDFMFLQSMGEG
AYSQVFRCREVATDAMFAVKVLQKSYLNRHQKMDAIIREKNILTYLSQECGGHPFVTQLYTHFHDQARIYFVIGLV
ENGDLGESLCHFGSFDMLTSKFFASEILTGLQFLHDNKIVHRDMKPDNVLIQKDGHILITDFGSAQAFGGLQLSQEGFT
DANQASSRSSDSGSPPPTRFYSDEEVPEENTARRTTFVGTALYVSPEMLADGDVGPQTDIWGLGCILFQCLAGQPPFR
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GEPEYYSNIGPVEPGLDDRALFRLMNLGNDASASQPSTFRPSNVEHRGDPFVSEIAPRANSEAEKNRAARAQKLEE
QRVKNPFHIFTNNSLILKQGYLEKKRGLFARRRMFLLTEGPHLLYIDVPNLVLKGEVPWTPCMQVELKNSGTFFIH
TPNRVYYLFDLEKKADEWCKAINDVRKRYSVTIEKTFNSAMRDGTFGSIYGKKKSRKEMMREQKALRRKQEKEE
KKALKAEQVSKKLSMQMDKKSP

Fig. 37

FIG. 38A

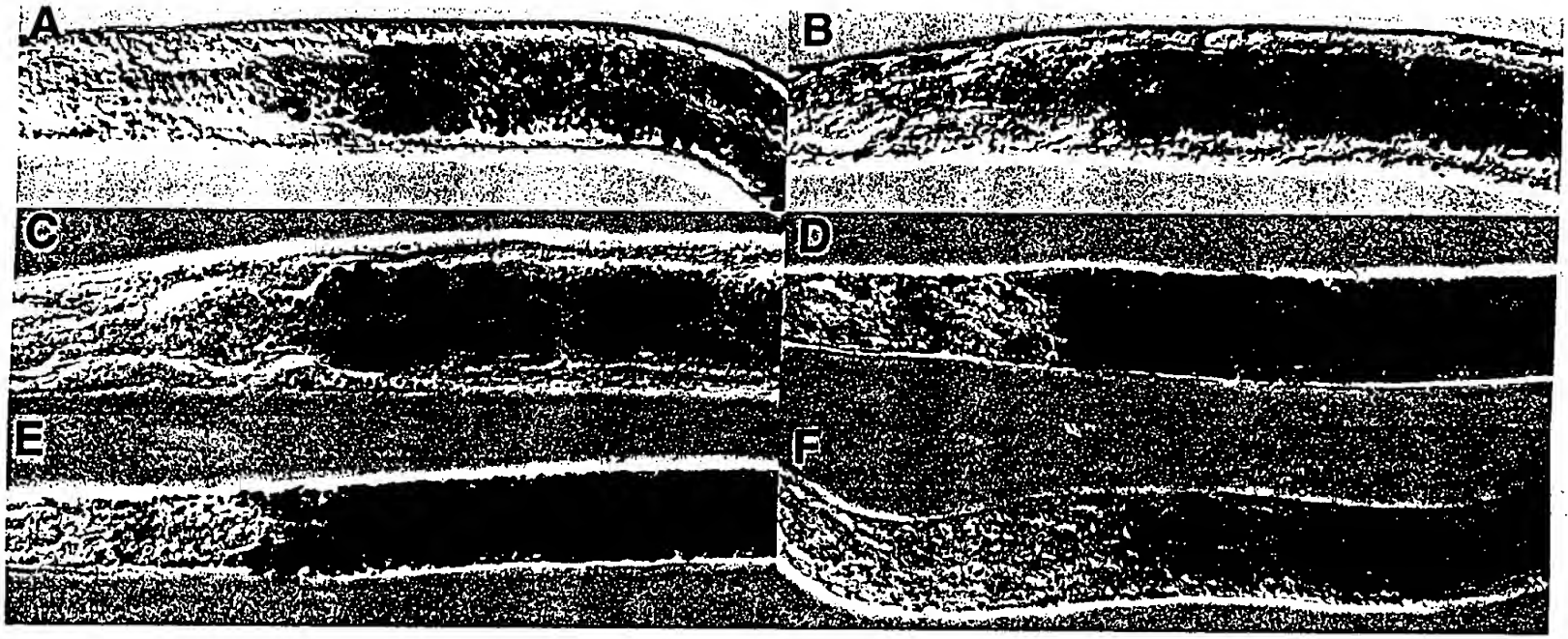

FIG. 38B

FIG. 38C

FIG. 38D

FIG. 38E

FIG. 38F

FIG. 39A

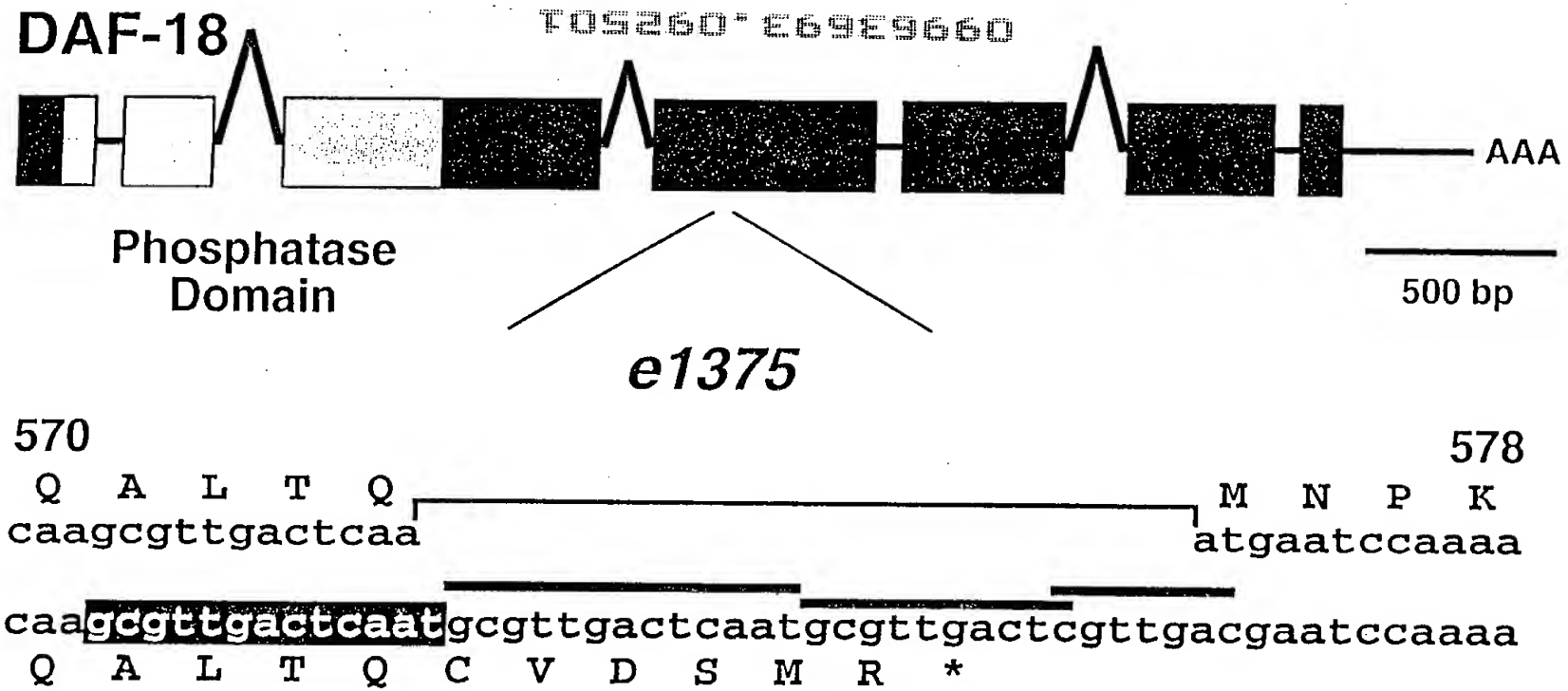

FIG. 39B

```
DAF-18   48 IFRTAVSSNR CRTEYQNIDL DCAYITDRII AIGYPATGIE ANFRNSKVQT
PTEN      4 TIKEIVSRNK RRYQEDGFDL DLTYIYPNII AMGFPAERLE GVYRNNIDDV

DAF-18   98 QQFLTRRHGK GNVKVFNLRG GYYYDADNFD GNVICFDMTD HHPPSLELMA
PTEN     54 VRFLDSKH.K NHYKIYNLCA ERHYDTAKFN CRVAQYPFED HNPPQLELIK

DAF-18  148 PFCREAKEWL EADDKHVIAV HCKAGKGRTG VMICALLIYI NFYPSPRQIL
PTEN    103 PFCEDLDQWL SEDDNHVAAI HCKAGKGRTG VMICAYLLHR GKFLKAQEAL

DAF-18  198 DYYSIIRTKN NKGVTIPSQR RYIYYYHKLR ERELNYLPLR MQLIGVYVER
PTEN    153 DFYGEVRTRD KKGVTIPSQR RYVYYYSYLL KNHLDYRPVA LLFHKMMFET

DAF-18  248 PPKTWGGGSK IKVEVGNGST ILFKPD..PL IISKSNHQRE RATWENNCDT
PTEN    203 IPMFSGGTCN PQFVVCQLKV KIYSSNSGPT RREDKFMYFE FPQPLPVCGD
```

DAF-18 Protein

MVTPPPDVPSTSTRSMARDLQENPNRQPGEPRVSEPYHNSIVERIRHIFRTAVSSNRCRTEYQNIDLDCAYITDRIIAIG
YPATGIEANFRNSKVQTQQFLTRRHGKGNVKVFNLRGGYYYDADNFDGNVICFDMTDHHPPSLELMAPFCREAKEWLEAD
DKHVIAVHCKAGKGRTGVMICALLIYINFYPSPRQILDYYSIIRTKNNKGVTIPSQRRYIYYYHKLRERELNYLPLRMQL
IGVYVERPPKTWGGGSKIKVEVGNGSTILFKPDPLIISKSNHQRERATWLNNCDTPNEFDTGEQKYHGFVSKRAYCFMVP
EDAPVFVEGDVRIDIREIGFLKKFSDGKIGHVWFNTMFACDGGLNGGHFEYVDKTQPYIGDDTSIGRKNGMRRNETPMRK
IDPETGNEFESPWQIVNPPGLEKHITEEQAMENYTNYGMIPPRYTISKILHEKHEKGIVKDDYNDRKLPMGDKSYTESGK
SGDIRGVGGPFEIPYKAEEHVLTFPVYEMDRALKSKDLNNGMKLHVVLRCVDTRDSKMMEKSEVFGNLAFHNESTRRLQA
LTQMNPKWRPEPCAFGSKGAEMHYPPSVRYSSNDGKYNGACSENLVSDFFEHRNIAVLNRYCRYFYKQRSTSRSRYPRKF
RYCPLIKKHFYIPADTDDVDENGQPFFHSPEHYIKEQEKIDAEKAAKGIENTGPSTSGSSAPGTIKKTEASQSDKVKPAT
EDELPPARLPDNVRRFPVVGVDFENPEEESCEHKTVESIAGFEPLEHLFHESYHPNTAGNMLRQDYHTDSEVKIAEQEAK
AFVDQLLNGQGVLQEFMKQFKVPSDNSFADYVTGQAEVFKAQIALLEQSEDFQRVQANAEEVDLEHTLGEAFERFGHVVE
ESNGSSKNPKALKTREQMVKETGKDTQKTRNHVLLHLEANHRVQIERRETCPELHPEDKIPRIAHFSENSFSDSNFDQAI
YL

FIG. 40A

```
   1 ttccaggtac atctactaac ccccaatggt tactcctcct ccagatgtgc caagcacatc
  61 gaccaggtcg atggctcgtg accttcaaga gaatccaaac cgacaacctg gtgaaccacg
 121 tgtgtctgaa ccgtatcaca attcaatcgt cgagcggatt cgccatattt ttcggacggc
 181 tgtatcttcc aatcgttgtc gcaccgagta ccaaaatatc gacctagatt gtgcatatat
 241 cacagaccga atcatagcta tcggttatcc agcaacagga atcgaagcga atttccgtaa
 301 ctcaaaagtt caaactcaac aatttctgac caggcggcac ggaaagggca acgtgaaggt
 361 gtttaacctg cgcggtggat actactacga tgcggataac ttcgatggaa atgttatttg
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 481 ggctaaggaa tggcttgaag cagacgataa acatgtaata gctgtacact gtaaagctgg
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 661 aattccatca caacgacgct acatttacta ctaccataag cttcgtgaac gtgagctcaa
 721 ctatttacca ttgagaatgc agttgattgg tgtctacgtg gaacggcctc caaagacatg
 781 gggtggtggt tcaaagataa aagtggaggt tggaaatggc tcgacaattt tatttaagcc
 841 ggatcctctc ataatctcca aatcaaatca tcagcgagag cgtgcgacgt ggctgaacaa
 901 ctgtgatacg cctaacgaat tcgacaccgg agagcaaaaa tatcatggat ttgtttccaa
 961 gagagcatac tgttttatgg tgccagaaga tgctccagta tttgtcgaag gagatgttcg
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1381 aaagcatgaa aaaggtatcg tcaaggatga ctataatgat cgtaagctgc caatgggaga
1441 caaatcatac acggaatcag gaaaaagtgg agatattcga ggagtcggtg gtccatttga
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1561 attgaagagt aaagatctta acaacggaat gaaacttcac gttgttcttc gttgtgtaga
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1681 tgaatcgaca cggaggcttc aagcgttgac tcaaatgaat ccaaaatggc gacctgaacc
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1861 cagaaatatt gccgttctta atcgatattg ccgatatttc tacaagcaac gcagtacatc
1921 tcgaagccgt tatccaagaa aattcagata ctgtcctctg atcaagaaac atttctacat
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2161 atccgacaag gtgaagccgg caactgaaga cgaacttcct cctgcgaggc taccggataa
2221 tgtgcgaaga tttccagtcg tcggcgttga tttcgaaaat ccggaagaag aatcgtgtga
2281 acacaaaacc gtagagtcaa tagctggttt tgaaccactc gaacatctat tccatgaatc
2341 ataccatcca aatacggccg gtaacatgct gcgtcaggat tatcacactg attcggaagt
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2521 aaccggacag gccgaagttt ttaaagcaca gattgcgtta ctggagcagt cggaggattt
2581 tcaacgagtt caagcgaatg cagaggaagt cgatcttgaa cacactcttg gtgaagcgtt
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2701 gaaaactcga gaacaaatgg tgaaagaaac tggcaaagac actcagaaga cccgcaatca
2761 tgtgcttcta catttggaag ctaatcatcg tgtgcaaatc gagcgtcgtg aaacgtgccc
```

FIG. 40B

2821 ggagctacat ccagaggata aaatcccaag aattgctcat ttttccgaaa acagcttctc
2881 ggattcgaat tttgatcaag ctatttattt gtaaacctaa aacaaaactt ttagaagatt
2941 ttcttcttac tgaccctcca attttcagat aatttcaatg ttttaagttt tctcttcaaa
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3061 tatattcata ttatagctct caacttcccg attttccacg tatatatgta tattttgccg
3121 ggtgaaaaat agcaattccc tatgaatgta tccccttcca tctgttttct tactcagaaa
3181 ttgtaattca cattgcgggt catcactaat cctatgggct ttaacacaat tctcccataa
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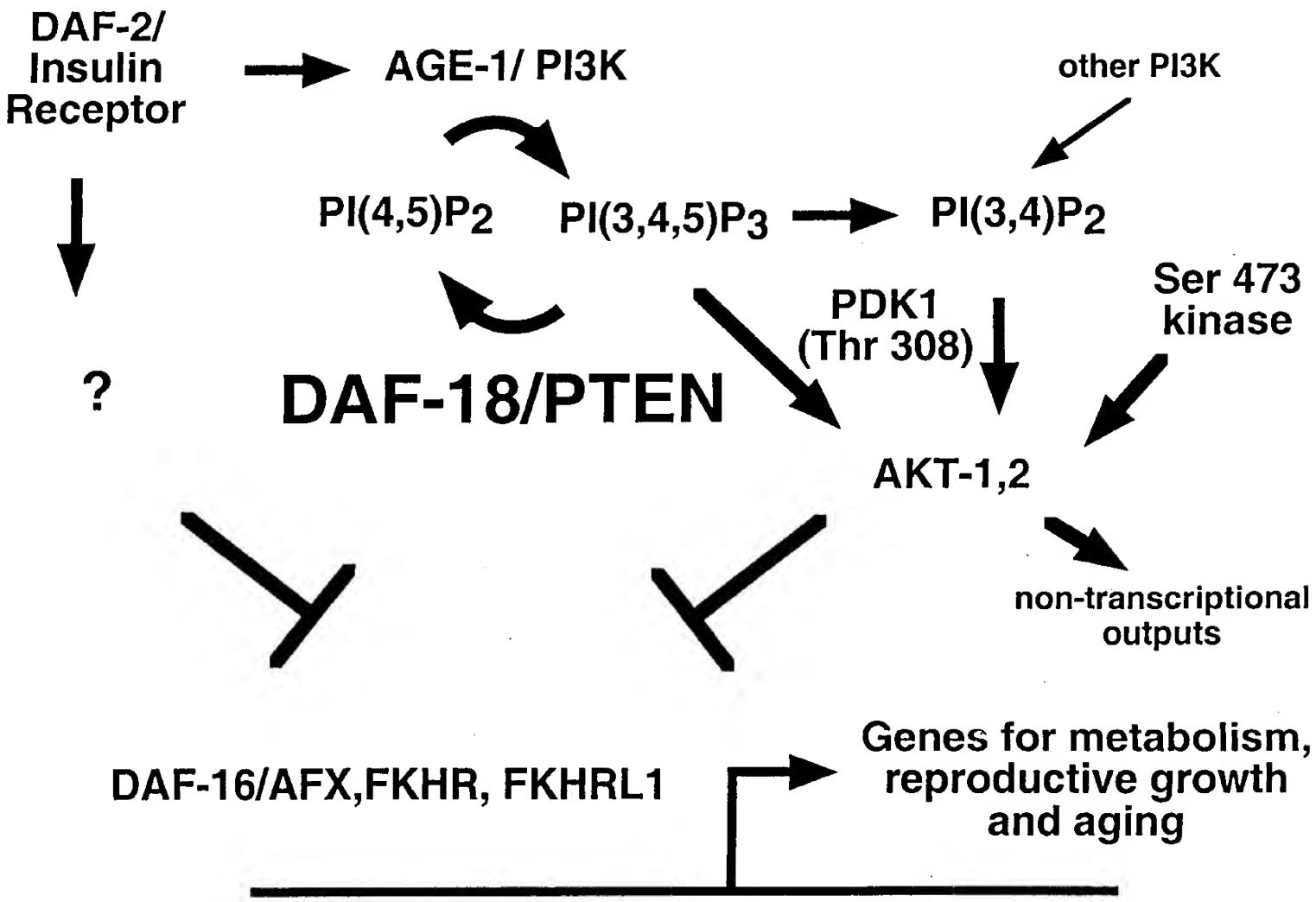
3301 ataa

FIG. 40B

FIG. 41


DAF-2/
Insulin
Receptor
AGE-1/ PI3K
other PI3K
PI(4,5)P2
PI(3,4,5)P3
PI(3,4)P2
PDK1
(Thr 308)
Ser 473
kinase
?
DAF-18/PTEN
AKT-1,2
non-transcriptional
outputs
DAF-16/AFX,FKHR, FKHRL1
Genes for metabolism,
reproductive growth
and aging

ttta

attacccaagtttgaggtagcattgctctcttcaatcat atg gat tcg ttg ttt cag atg gca tcc gca
M D S L F Q M A S A

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M K F Q Y Y S K K A A G K T M S N S V S

atg tcc agt gac aat cgc atg gag gat ttt aaa cgt cgt ttt cgt cga agt gga tcg tta
M S S D N R M E D F K R R F R R S G S L

gga att cca ttt gtc cca gaa gaa gat gtt aaa caa ctc ttc aca cca act cgt act gtt
G I P F V P E E D V K Q L F T P T R T V

cgt cga gaa gca tct att cgc gaa ggg gat gag gaa gaa gga gta caa att ctc aca ata
R R E A S I R E G D E E E G V Q I L T I

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I V K S S R V S E D I S K M I A N L P D

cac act cgt atc aaa cat ttg gag act cgt gac agt caa gat gga agt tcc aaa act atg
H T R I K H L E T R D S Q D G S S K T M

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D V L L E I E L F H Y G K Q E A M D L M

aga ctt aat ggg ctt gat gtt cat gag gtg tca tcg act att cgt cca act gca ata aaa
R L N G L D V H E V S S T I R P T A I K

gag caa tat aca gag cct gga tct gat gat gcg aca acc ggt tct gaa tgg ttt cca aaa
E Q Y T E P G S D D A T T G S E W F P K

agt att tat gat ttg gat att tgt gca aaa aga gtg att atg tat gga gca ggg ctg gac
S I Y D L D I C A K R V I M Y G A G L D

gct gat cat cct ggt ttc aaa gat acc gag tat cgt caa cgt cga atg atg ttt gct gaa
A D H P G F K D T E Y R Q R R M M F A E

ctg gcg ctc aat tac aaa cac ggt gag cca att ccg cga acc gaa tat aca tca tcc gaa
L A L N Y K H G E P I P R T E Y T S S E

cgg aaa act tgg gga att ata tat aga aaa ttg aga gaa ttg cac aaa aag cac gca tgc
R K T W G I I Y R K L R E L H K K H A C

aag cag ttt ctt gat aac ttt gag cta ctg gag aga cat tgt gga tac tcg gaa aat aat
K Q F L D N F E L L E R H C G Y S E N N

att ccg caa cta gaa gat atc tgc aag ttt ttg aaa gca aaa act gga ttc cgt gtt cgc
I P Q L E D I C K F L K A K T G F R V R

FIG. 42

```
cca gtc gcc gga tac tta tca gct cgt gat ttc ttg gca ggt ctt gca tat cgt gtc ttc
P   V   A   G   Y   L   S   A   R   D   F   L   A   G   L   A   Y   R   V   F

ttc tgc act caa tac gtt cgc cat cat gcc gat cca ttt tac act cca gaa cca gac acc
F   C   T   Q   Y   V   R   H   H   A   D   P   F   Y   T   P   E   P   D   T

gtt cac gag ctc atg ggt cac atg gct cta ttc gct gat cca gat ttt gct cag ttt tct
V   H   E   L   M   G   H   M   A   L   F   A   D   P   D   F   A   Q   F   S

caa gag att gga tta gct tct ctt gga gca tca gag gaa gat ttg aag aag ctt gca aca
Q   E   I   G   L   A   S   L   G   A   S   E   E   D   L   K   K   L   A   T

ctc tac ttc ttt tcc att gaa ttt ggt ctc tcg tct gat gac gct gcc gat tct cca gta
L   Y   F   F   S   I   E   F   G   L   S   S   D   D   A   A   D   S   P   V

aaa gaa aat gga tca aat cat gaa aga ttt aaa gta tac gga gca gga ctt ctg agc agt
K   E   N   G   S   N   H   E   R   F   K   V   Y   G   A   G   L   L   S   S

gct ggc gag ttg caa cat gcc gtt gag ggt agt gca acc att att cgt ttt gat ccg gat
A   G   E   L   Q   H   A   V   E   G   S   A   T   I   I   R   F   D   P   D

cgt gtt gtt gag caa gaa tgt ctc att act act ttc cag tca gcg tat ttc tat act aga
R   V   V   E   Q   E   C   L   I   T   T   F   Q   S   A   Y   F   Y   T   R

aat ttt gaa gag gcc cag cag aaa ctc aga atg ttc acc aac aac atg aaa cgt ccc ttc
N   F   E   E   A   Q   Q   K   L   R   M   F   T   N   N   M   K   R   P   F

att gtt cgt tac aac cca tac aca gaa agc gtc gaa gtt ctc aac aac tcc cgt tcc att
I   V   R   Y   N   P   Y   T   E   S   V   E   V   L   N   N   S   R   S   I

atg ttg gca gtg aac tct ctc cgc tca gac atc aac ctg ctc gcc gga gct ctc cac tac
M   L   A   V   N   S   L   R   S   D   I   N   L   L   A   G   A   L   H   Y

atc ctg tag
I   L   *
```

FIG. 42

attacccaagtttgaggtagcattgctctcttcaatcat

```
atg gat tcg ttg ttt cag atg gca tcc gca atg aag ttt caa tac tac tcg aag aaa gct
M   D   S   L   F   Q   M   A   S   A   M   K   F   Q   Y   Y   S   K   K   A

gct gga aag aca atg tct aat agt gtc aaa aac tgg att ccg tgt tcg ccc agt cgc cgg
A   G   K   T   M   S   N   S   V   K   N   W   I   P   C   S   P   S   R   R

ata ctt atc agc tcg tga ttt ctt ggc agg tct tgc ata tcg tgt ctt ctt ctg cac tca
I   L   I   S   S   *

ata cgt tcg cca tca tgc cga tcc att tta cac tcc aga acc aga cac cgt tca cga gct

cat ggg tca cat ggc tct att cgc tga tcc aga ttt tgc tca gtt ttc tca aga gat tgg

att agc ttc tct tgg agc atc aga gga aga ttt gaa gaa gct tgc aac act cta ctt ctt

ttc cat tga att tgg tct ctc gtc tga tga cgc tgc cga ttc tcc agt aaa aga aaa tgg

atc aaa tca tga aag att taa agt ata cgg agc agg act tct gag cag tgc tgg cga gtt

gca aca tgc cgt tga ggg tag tgc aac cat tat tcg ttt tga tcc gga tcg tgt tgt tga

gca aga atg tct cat tac tac ttt cca gtc agc gta ttt cta tac tag aaa ttt tga aga

ggc cca gca gaa act cag aat gtt cac caa caa cat gaa acg tcc ctt cat tgt tcg tta

caa ccc ata cac aga aag cgt cga agt tct caa caa ctc ccg ttc cat tat gtt ggc agt

gaa ctc tct ccg ctc aga cat caa cct gct cgc cgg agc tct cca cta cat cct gta g
```

FIG. 43

FIG. 44A

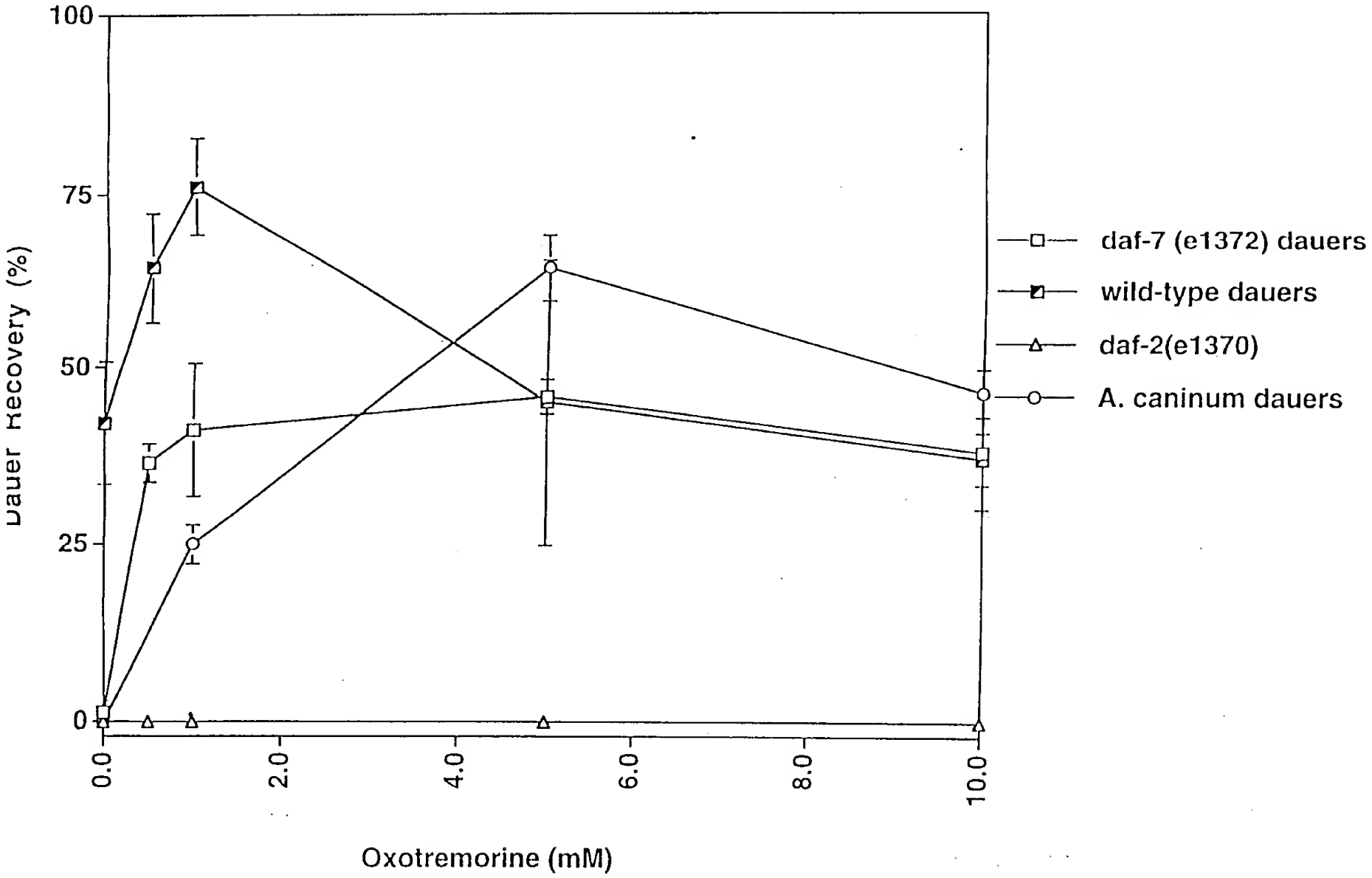


FIG. 44B

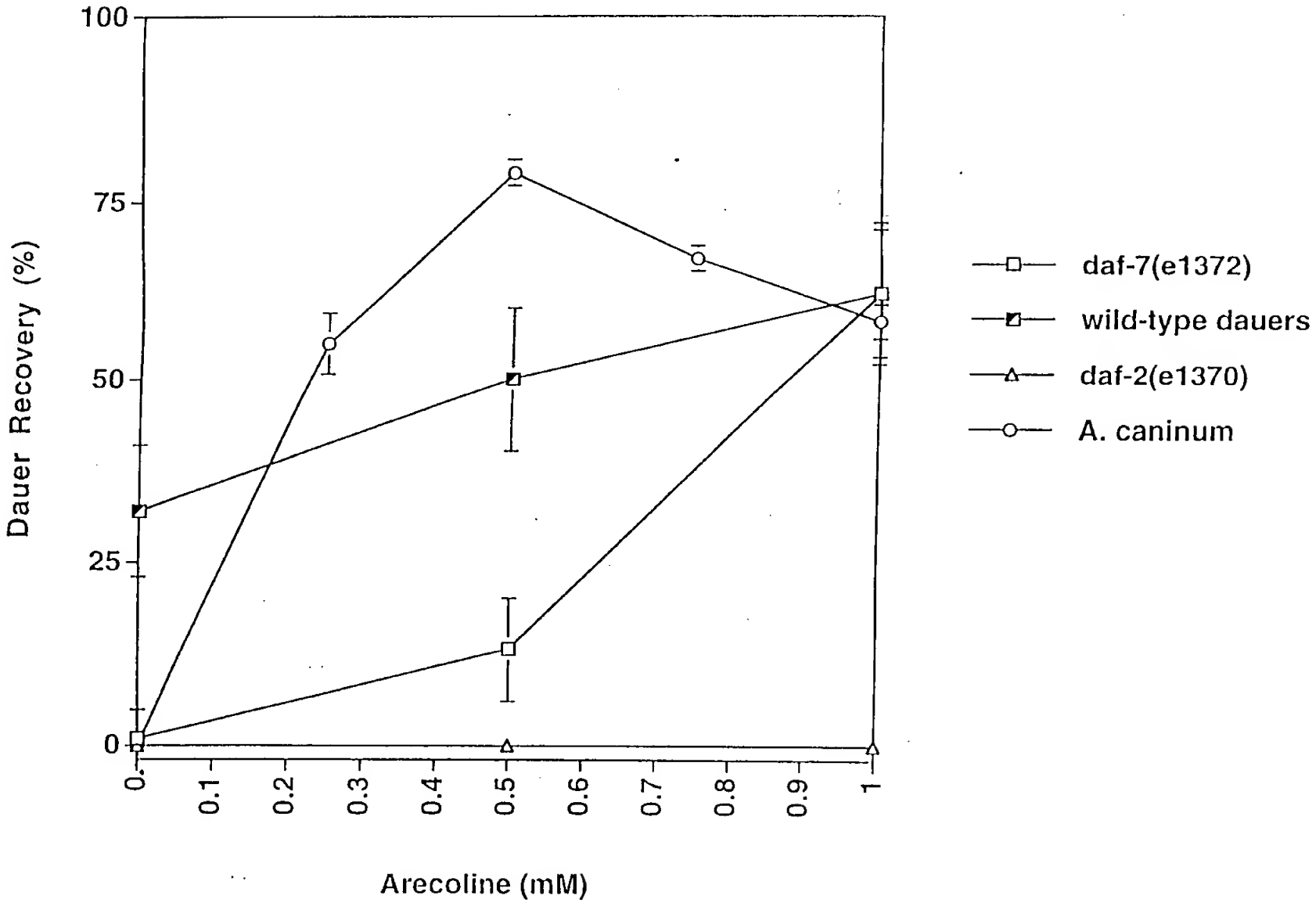


FIG. 45A

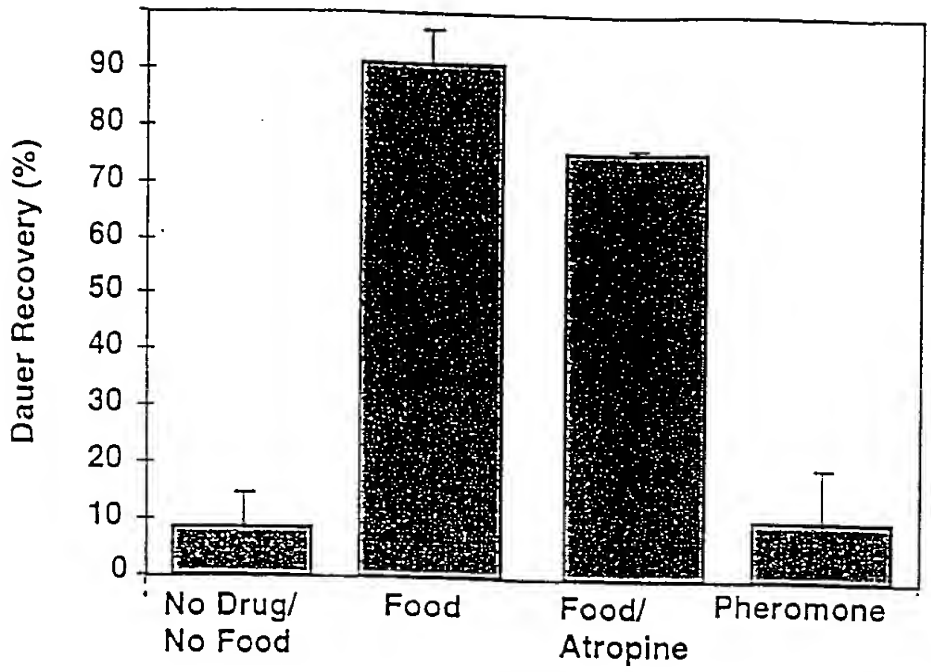

Dauer Recovery (%)
90
80
70
60
50
40
30
20
10
0
No Drug/
No Food
Food
Food/
Atropine
Pheromone

FIG. 45B

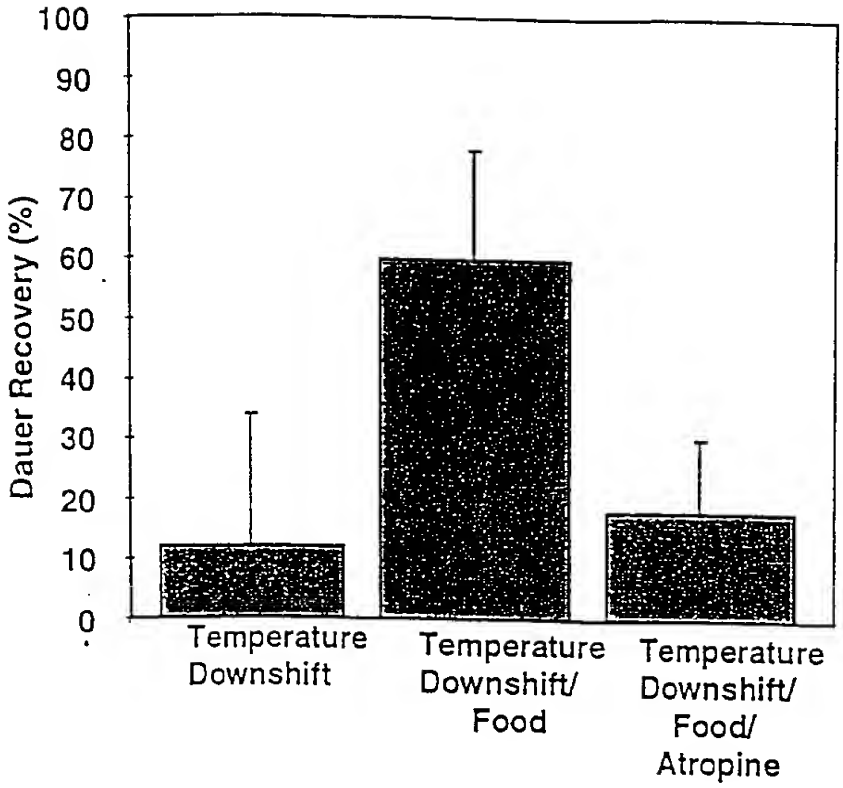

Dauer Recovery (%)
100
90
80
70
60
50
40
30
20
10
0
Temperature Downshift
Temperature Downshift/ Food
Temperature Downshift/ Food/ Atropine

FIG. 44C

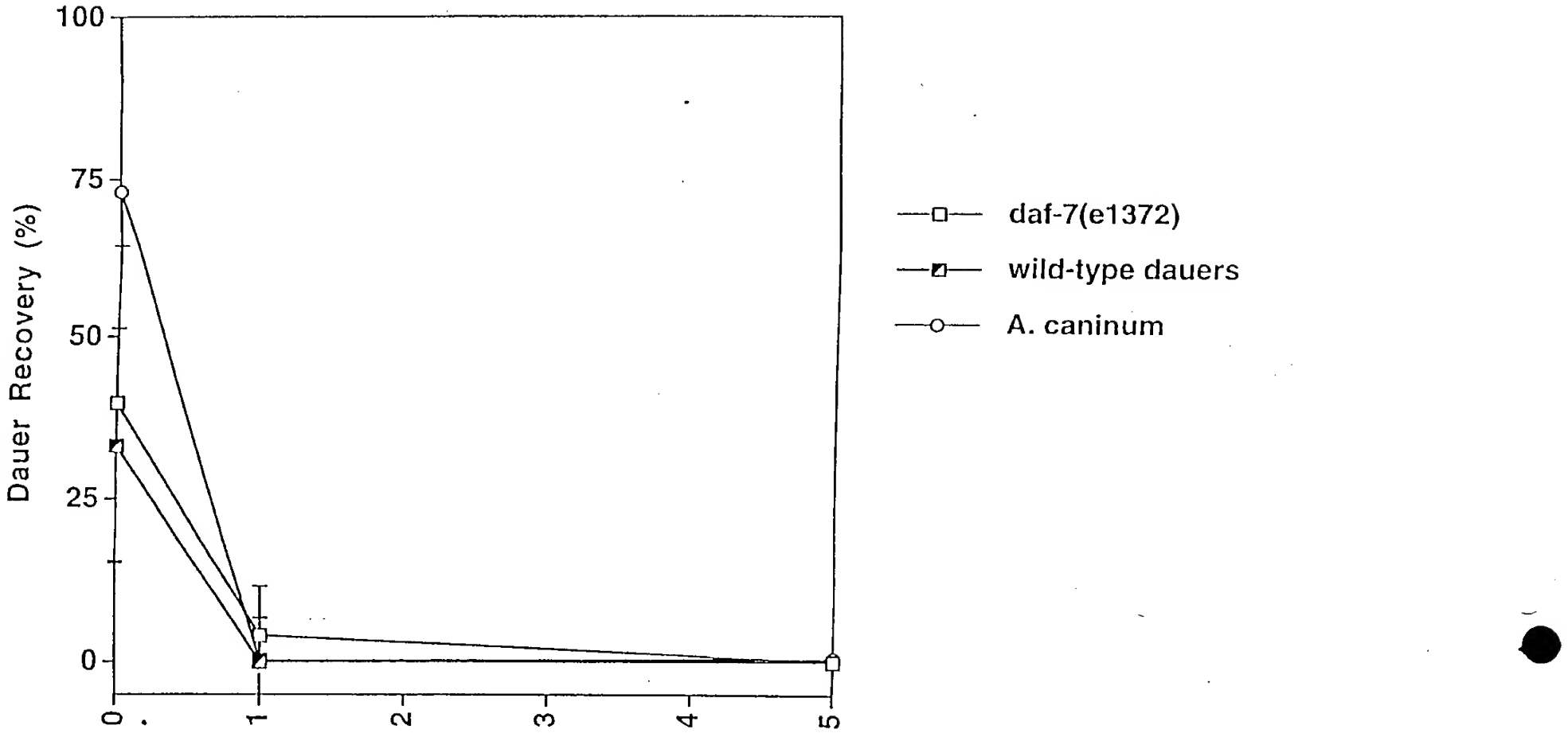
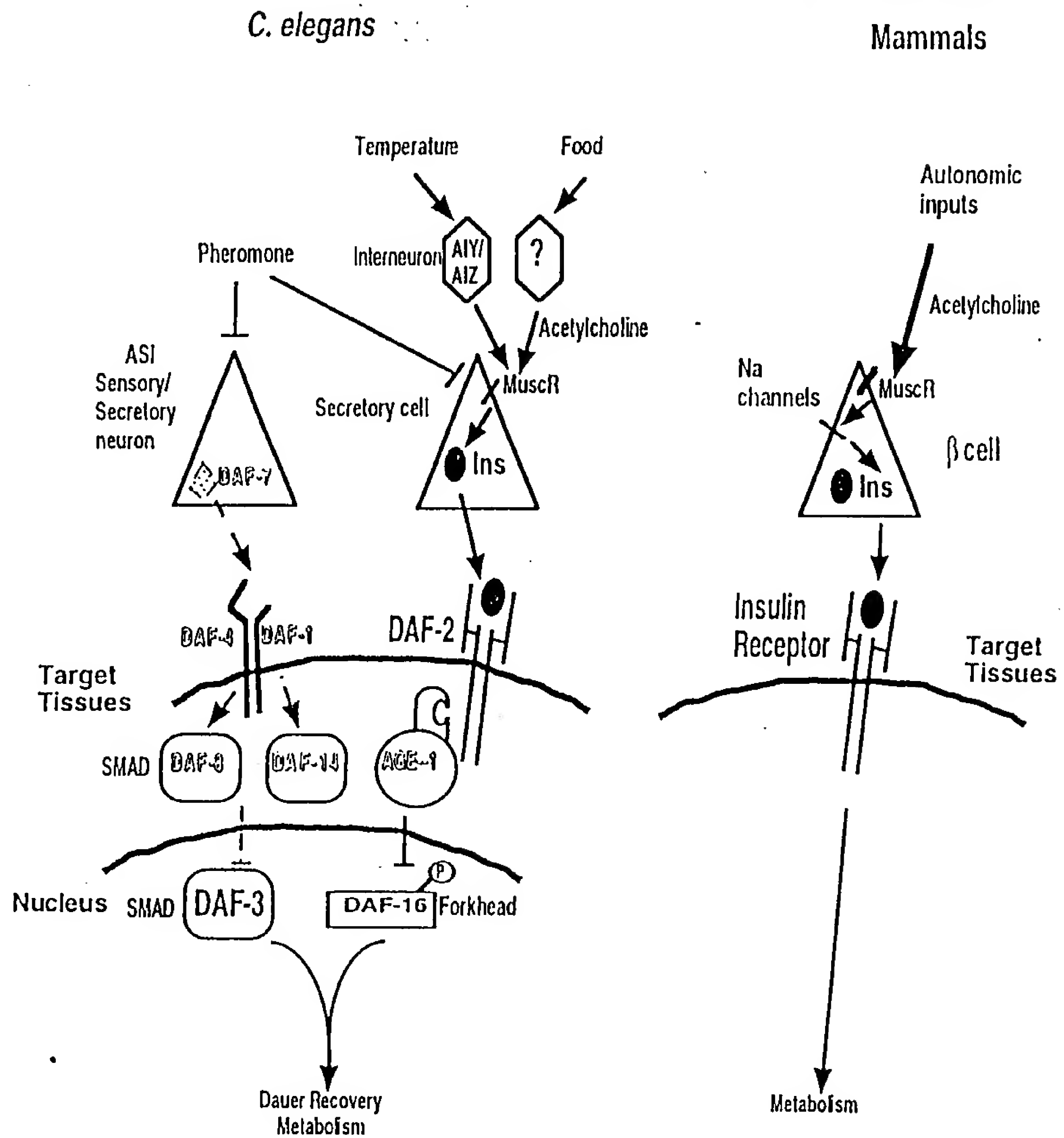


FIG. 46


C. elegans
Mammals
Temperature
Food
Pheromone
Interneuron
AIY/ AIZ
?
Acetylcholine
ASI Sensory/ Secretory neuron
Secretory cell
MuscR
DAF-7
Ins
DAF-4
DAF-1
DAF-2
Target Tissues
SMAD
DAF-8
DAF-14
AGE-1
Nucleus
DAF-3
DAF-16
Forkhead
P
Dauer Recovery Metabolism
Autonomic inputs
Acetylcholine
Na channels
MuscR
β cell
Ins
Insulin Receptor
Target Tissues
Metabolism

ATTCGGCATGAGCATGGaGCTTCGAGTCCTAGAGAACACAAAACGTTCCCGGCGGAACCTGGGtCTGGACTGCGAC
GAGACTCAAGCGAGTCCCGCTGCTGCCGATATCCCCTCACAGTGGACTTTGAGGCTTTCGGCTGGGACTGGATCAT
CGCACCTAAGCGCTACAAGGCCAACTACTGCTCCGGCCAGTGGGAGTACATGTTCATGCAAAAATATCCGCATACC
CATTTGGTGCAGCAGGCCAATCCAAGAGGTTATGcTGGGCCCTGTTGTACCCCCACCAAGATGTCCCCAATcAACA
TgcTctACTTCAATGACAAGCAGCAGATTATcTACGGCAAGATCCCTGGCATGGTGGTGGATCGCTGTGGcTGCTC
TTAAGGTGGGGGATAGAGGATGCCTCCCCCACAGACCGTACCCCAAGACCCATAGCCcTGCCCAATCCACCGCCTG
ATCCAAACAT

FIG. 47A

IRHEHGASSPREHKTFPAEPGSGLRRDSSESRCCRYPLTVDFEAFGWDWIIAPKRYKANYCSGQWEYMFMQKYPHT
HLVQQANPRGYAGPCCTPTKMSPINMLYFNDKQQIIYGKIPLAMVVDRCGCS

FIG. 47B